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VOL. XXXV JANUARY 1951 FASC. 1

CARCINOMA OF THE HYPOPHARYNX[1]

A clinical study of 322 cases, treated at Radiumhemmet, from 1939 to 1947

by

Folke Jacobsson

In this study the term hypopharyngeal cancer is used to include all carcinomas from the valleculae to the upper part of the oesophagus, except the intrinsic laryngeal carcinomas. The borderline between the larynx and the hypopharynx has been drawn at the laryngeal inlet, that is, the edge of the epiglottis, the ary-epiglottic folds and the arytenoid region.

Growths originating at the junction of the hypopharynx and the oesophagus, at the level of the sixth cervical vertebra, are also classified as hypopharyngeal carcinomas. In most cases it is difficult to decide the point of origin, and from the radiotherapeutic point of view, these tumours are more closely related to carcinomas of the hypopharynx than to oesophageal carcinomas.

We have classified cancer of the hypopharynx in two groups, carcinomas of the upper and carcinomas of the lower portion of the hypopharynx. The borderline between the groups has been drawn at the superior border of the cricoid cartilage. The reasons for this division are differences in prognosis, sex distribution and predisposing factors.

Thus the first group includes carcinomas situated in the external portions of the larynx and the pyriform fossa. All other carcinomas are referred to the other group.

Clinical material

At Radiumhemmet, in the years 1939 to 1947, we have treated 322 cases of carcinoma of the hypopharynx. Of these, 119 were men and 203 women.

[1] This investigation was aided through grants from P. A. Ljungberg's and Lotten Bohman's Foundations.

Submitted for publication, Sept. 19, 1950.

From Radiumhemmet (Director: Professor Elis Berven), Stockholm, Sweden.

During the same time 53 cases were not accepted for treatment, on account of too advanced stage of disease (14 per cent).

The result of treatment is known in every case and the observation period for all patients is at least two years.

Table I.

Shows the distribution of patients in the different years

Year	Accepted	Not accepted
1939	37	7
1940	38	7
1941	44	5
1942	38	4
1943	33	3
1944	33	5
1945	33	8
1946	30	5
1947	36	9

Age distribution

Table II.

Shows the distribution according to age

Age	Men	Women
20—29 years	3	0
30—39 »	3	10
40—49 »	16	47
50—59 »	41	72
60—69 »	36	56
70—79 »	18	18
80— »	2	0

Most cases occurred after 50 years of age, and approximately 2/3 between 50 and 69 years of age. *Nearly 1/4 of the patients, however, were less than 50 years of age.* The youngest patient was 26 and the oldest 81 years old, both being men.

Sex distribution

One hundred and nineteen of the patients were men and 203 women (60 per cent women).

It seems evident that there is a rather high proportion of women with cancer of the hypopharynx in Ireland, Norway, Scotland and Sweden (40—60 per cent women), as compared with other countries. In France and Switzerland, carcinoma of the hypopharynx in women is very rare.

Table III.

Shows the percentage of women according to statistics from different countries

Country	Percent of women
France (BACLESSE)	1
Switzerland (SCHINZ & SENTI)	9
U. S. A. (MARTIN)	15
Denmark (VIDEBÆK)	20
England (CADE)	25
Finland (SIPILÄ)	30
Ireland (DOUGLAS)	40
Norway (RENNÆS)	50
Scotland (TURNER)	55
Sweden (*Radiumhemmet*)	60

Differences in sex distribution by site

Reports from different countries show that carcinoma in the upper part of the hypopharynx is predominantly found in males (70—90 per cent men). In the lower part, on the other hand, there is a preponderance in the female sex (50—80 per cent women).

At Radiumhemmet, cancer in the upper part of the hypopharynx was found in men in 85 per cent of the cases. In the lower part, only 20 per cent of the cases were males.

Frequency of cancer in upper and lower part of hypopharynx

In about 3/4 of our cases the tumour was situated in the lower part of the hypopharynx. In diffuse tumours there may be difficulties in defining the point of origin. The previous history and clinical examination throughout the course of treatment are often of great help.

Table IV.

Shows the approximate proportion of carcinomas of the lower part of hypopharynx in reports from different countries

Country	Per cent carcinomas of lower part of hypopharynx
England	25
Finland	25
Ireland	35
Norway	40
Scotland	50
Sweden	75

As could be expected from the differences in sex distribution, there is a rather high proportion of carcinomas in the lower part of the hypo-

pharynx in Ireland, Norway, Scotland and Sweden, as compared with other countries. In France, carcinoma in the lower part is very rare.

Predisposing factors

The factors considered to be of special importance for the development of cancer of the hypopharynx are: sideropenia (the Plummer-Vinson syndrome), misuse of alcohol and heavy smoking.

Sideropenia
(*The Plummer-Vinson syndrome*)

AHLBOM (1941) has pointed out the frequent occurrence of sideropenia in Swedish women with cancer of the hypopharynx. He considered the secondary changes of the hypopharyngeal mucosa, developing in sideropenia, as a precancerous condition.

In our cases, 90 per cent of the women and about 10 per cent of the men showed definite signs and symptoms of sideropenia.

In Norway (RENNÆS) and Scotland (TURNER) sideropenia, or the Plummer-Vinson syndrome, was found in 30—40 per cent of women with hypopharyngeal carcinoma. According to DOUGLAS a very high percentage of women in Ireland, with post-cricoid carcinoma, show the Plummer-Vinson syndrome. In Denmark, on the other hand, sideropenia (VIDEBÆK) is very rare. BACLESSE in France and SCHINZ in Switzerland (personal communications) have not seen any patients with sideropenia and hypopharyngeal cancer.

It seems that the occurrence of sideropenia is attributed to hereditary factors (LUNDHOLM and WALDENSTRÖM), and unsuitable diet (vitamin and iron deficiency etc.). Sideropenia is predominantly a disease of poor people. In his private practice, AHLBOM found only about 4 per cent of women with sideropenia.

WALDENSTRÖM (1946) has proposed the theory that it is not the iron content of the food that is of importance in the development of sideropenia, as much as other factors which tend to keep the serum iron at a higher or lower level.

Alcohol and tobacco

Excessive use of alcohol will not readily be admitted by the patient. When questioned, he often states that his consumption of alcohol is very moderate. The best way to get reliable information is to ask members of his family.

In our cases, 63 of 99 men questioned admitted use of alcohol, and of these, 35 used alcohol in excess (about 1/3 of all male patients). Most of these patients were also heavy smokers. Another 19 male patients ad-

mitted only heavy smoking, and they all had carcinoma in the upper part of the hypopharynx.

There is no reason to believe that any appreciable number of women used alcohol, at least to excess.

It is interesting that in some chronic alcoholics we have found a low serum iron value. The sideropenia in these cases was probably due to unsuitable diet, in connection with misuse of alcohol.

Duration and diagnosis

In about 1/3 of our cases the duration of symptoms was more than 6 months. The initial symptoms are often neglected by the patient. Men may have a long previous history of pharyngitis, and women one of sideropenic dysphagia. These patients are used to intermittent periods of increased discomfort in swallowing.

In some cases, however, the diagnosis was delayed by the doctor first consulted.

As a rule the diagnosis of a carcinoma in the upper part of the hypopharynx is not difficult. Tumours arising in the pyriform fossa, however, cause few or no symptoms, and may develop to a considerable degree before causing sufficient trouble to attract the patient's attention. In many cases the appearance of large lymph node metastases, below the angle of the jaw, is the first symptom noticed.

The diagnosis of a carcinoma in the lower part may be impossible without special methods of investigations, such as roentgen and endoscopic examination. *The tumour was invisible on indirect laryngoscopy in 1/6 of our cases.*

Site, size and extension of primary tumour

The site of origin was considered to be in the pyriform fossa in about 3/4 of our cases of cancer in the upper part of the hypopharynx, and in the other cases, in the external portions of the larynx.

The disease had extended to the oesophagus in about 2/3 of our carcinomas of the lower part of the hypopharynx.

The extension of the tumour in the hypopharynx was more than 5 cm in forty-five per cent of the cases, and a tumour length of 8—10 cm was not unusual.

Metastases

Clinical lymph node metastases were present in 54 per cent of our cases. The involved nodes were inoperable on admission in about fifty per cent of the cases.

Lymph node metastases were found in 64 per cent of carcinomas of the upper part of the hypopharynx, and in 50 per cent of carcinomas of the lower part.

CADE found metastases in 60 per cent of carcinomas in the upper part, and in 50 per cent of carcinomas of the lower part, approximately the same figures as in our series.

Distant metastases were noticed in 18 of our cases, and in 7 of these, skeletal metastases had developed.

Histology

Microscopic verification of the clinical diagnosis was made in all our cases, except one. In this case, a two-year cure, no biopsy was taken. The tumour was situated in the upper part of the hypopharynx, and the patient presented a very typical clinical picture and was therefore included in the material, in spite of the absence of microscopic verification.

Well differentiated squamous-cell carcinoma was the predominant morphologic type found in our cases. Poorly differentiated carcinomas were found in 1/3 of the cases of the upper part of the hypopharynx, but in only 1/10 of the cases in the lower part.

Choice of method of treatment

In suitable, selected cases, surgical removal of hypopharyngeal carcinoma is possible. On the whole, however, surgery accounts for but few successes, and it is not applicable to any but the earliest cases. GRAHAM has reported a 24-year survival after operation of a post-cricoid carcinoma. It must also be emphasized that operation means pharyngectomy and in many cases also laryngectomy.

In the majority of cases, radiological methods offer the only hope of cure.

Teleradium, which at Radiumhemmet is considered the method of choice in early cases of intrinsic laryngeal carcinomas, is of limited value in the treatment of our hypopharyngeal carcinomas. Teleradium, as the only treatment method, has been employed in only 14 of the present cases. In all these cases the tumour was situated in the upper part of the hypopharynx, and was of rather limited extension. It is difficult, with the many ports of entry indispensable in teleradium treatment of a large, bulky hypopharyngeal tumour, to obtain a homogeneous tumour and tissue dosage. It is also difficult to avoid unintentional irradiation of the medulla.

Teleradium, as complementary treatment of lymph node metastases has, however, been of great value in many cases.

The greatest advance in the technique of *roentgen treatment* was made by COUTARD, through the introduction of the fractional method of treatment, in the years previous to 1930, with doses of a magnitude unbelievable at that time. In 1935 COUTARD could report several five-year cures. However, the violence of the local reactions, often dangerous in feeble patients, who sometimes succumbed to laryngeal oedema, necrosis of cartilage and broncho-pneumonia, made it necessary to change the technique. According to BACLESSE, the guiding principle at present, at the Fondation Curie, is to avoid reactions, but nevertheless to increase the total dose. This has led to protraction of treatment and diminution of the size of fields. The overall treatment time has been extended to six to twelve weeks.

In four of COUTARD's successful cases, treated in 1932—1933, the intense treatment resulted in a roentgen-cancer in the mucosa 6—10 years after treatment (BACLESSE).

Fractionated roentgen treatment of hypopharyngeal carcinoma has been used at Radiumhemmet since 1930, and is considered as the method of choice. The roentgen technique has varied within certain limits, especially in regard to the number and location of the fields. As the result of an analysis of our cases up to 1939 (AHLBOM, 1941), it became clear that the total tumour dose over a certain number of days was the factor of decisive significance in the radiation treatment of hypopharyngeal carcinoma. The importance of protecting the healthy tissues surrounding the tumour from intense radiation was also stressed. It was also evident that some patients had developed a radiation injury of the cervical spinal cord (myelodegeneration). Keeping all these circumstances in mind, we modified our treatment technique in 1943.

Treatment technique

The first thing to do, after the clinical diagnosis has been established, is to ascertain accurately the size, extent and localization of the tumour. The roentgen examination reveals the extent of the tumour and indicates the degree of invasion by the tumour into the normal surrounding tissues. Direct endoscopic examination shows the gross anatomical appearance of the carcinoma. It is important to get an impression of the mode of growth of the tumour. As a rule, a superficially growing, non-infected, papillary growth may be radiated more intensely than an infiltrating, infected and ulcerated tumour.

The roentgen treatment is carried out with the patient in sitting position. We use a chair, specially constructed for the purpose (LUNDSTRÖM), in which the patient is rather comfortable during the treatment. In order to eliminate the cervical lordosis, the patient's head is slightly bent for-

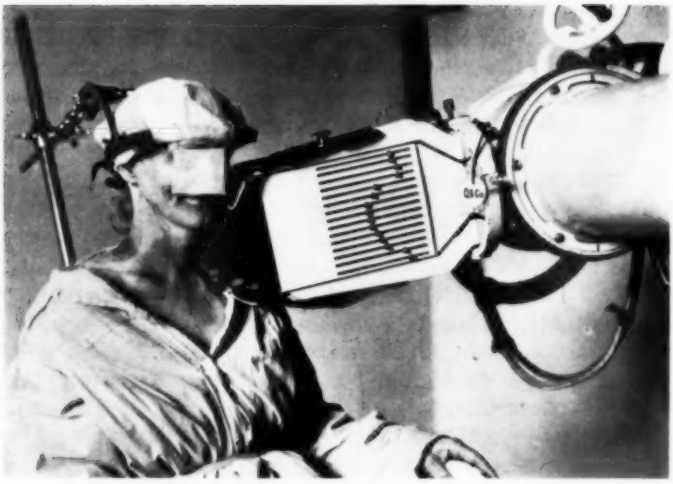

Figure 1. Patient in treatment position. The ribs of the diaphragm are well adjusted to the curved treatment fields. The size of the fields can be seen, due to beginning skin reaction.

ward and fixed in this position with straps. Thus it is easier to avoid unintentional irradiation of the cervical spinal cord (Figure 1).

The treatment is given by means of a special diaphragm (earlier described by LUNDSTRÖM, 1943), adjustable to the curved skin surface. *The beam is directed through fluoroscopy.*

We use a cross-fire technique with four fields, one anterior and one posterior, on each side of the neck. The fields are rather narrow, 3.5—4 cm, but extend in most cases from the edge of the lower jaw down to, or often several centimeters below, the clavicle.

The treatment is given with about 180 kv and 1/2 mm of copper, at a distance of 60 cm. The intensity is about 50 r per minute, measured on the surface of the skin. One field is treated each day, and thus each field is irradiated every fourth day. The daily skin dose is usually 400—500 r, including back-scatter.

A diagram of a transverse section of the neck, at the level of the mid-portion of the tumour, is made in every case. Thus the relative position of the fields and the directions of the beams are shown (Figure 2). The tumour doses are calculated with the aid of this diagram, but from time to time checked by direct measurements by the insertion of SIEVERT's condensor chambers into the hypopharynx.

In the mid-portion of the neck, the depth dose obtained through

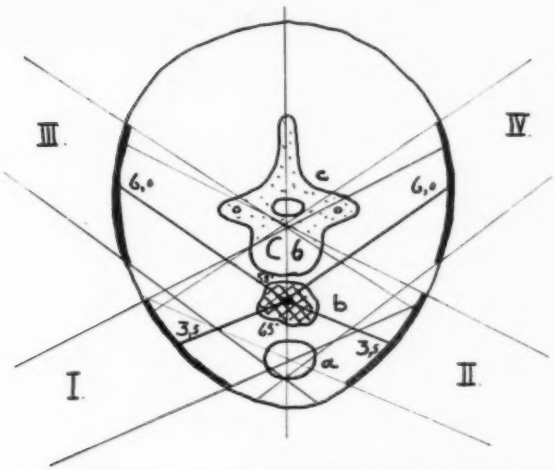

Figure 2. Diagram of a transverse section of the neck, at the level of the sixth cervical vertebra (c). Trachea at a. Distances in centimeters between center of tumour (b) and centers of treatment fields (I, II, III, IV).

the anterior fields is about 60—75 per cent of the surface dose, and through the posterior fields, 40—45 per cent.

We have found that the total tumour dose required to produce a complete regression of the tumour is about 5,700—6,000 r given over a period of about one month. To achieve this, each field receives 2,600—3,000 r.

The skin reaction, with this dose, usually is only a dry epidermitis, with an exudative dermatitis in parts of the fields. The permanent skin changes are, as a rule, very moderate. There is a slight pigmentation and atrophy of the skin 5—6 years after the treatment, as shown from Figure 3, with some teleangiectasia. The skin is soft and pliable.

The mucosal reaction in the hypopharynx appears 2—4 weeks after the beginning of the treatment. We feel that a fibrinous reaction (epithelitis), well centered over the tumour, is of great advantage for the tumour healing, partly due to the accompanying hyperemia in the tumour.

In an impaired condition of the patient, and in cases with large, infected tumours, it is necessary to begin radiation cautiously, and only gradually increase the doses. Thus it usually is possible to avoid acute oedema and the necessity of emergency tracheotomy or gastrostomy. *Penicillin is of great benefit in this connection, as well as a rich supply of, parenterally administered, glucose, amino-acids, vitamines and iron (in cases with sideropenia)*. We have also noticed the benefit of whole-blood transfusions.

Figure 3. Skin changes six years after roentgen treatment. Total tumour dose about 6,200 r in 33 days. The patient, 51 years old on admission, has been well and free from signs and symptoms for nearly seven years. No complications during or after the treatment.

In tumours of great lengths, the difference in depth of the upper and lower part of the tumour may be great. In such cases, when the necessary tumour dose has been reached in the upper part of the tumour, the corresponding parts of the treatment fields may be covered. The treatment is then continued through the remaining parts of the fields, until the required dose has been obtained in the lower part of the tumour. In many of these cases it is necessary to give additional treatment through an extra field in the anterior midline.

In the presence of lymph node metastases, teleradium is often used in addition to roentgen treatment. In the case with large metastases, it may be necessary to use a technique specially suited to the case in hand.

The teleradium treatment is given through portals with a diameter of 5 cm, and a distance between the centre of the treatment fields of 6—7 cm. Daily treatments for 1½—2 hours, corresponding to 900—1,000 teleradium-r, are given with a 3 or 5 gram apparatus.

Results of treatment

The duration of disease, without treatment, from the first symptoms until death, seems to be rather short in most instances. It has been possible to obtain information on the survival in 24 untreated cases. All but three died within one year, and fifty per cent of these patients during

the first half year. The longest survival time was one year and four months.

It is impossible, even with irradiation, to obtain a cure or prolonged survival in more than a minority of the cases, due to the advanced stage of the disease and the poor general condition on admission. In 1/3 of our cases it was impossible to give a full treatment series.

In the literature, the prognosis is considered to be relatively better in cases of cancer of the upper than of the lower part of the hypopharynx. Among the patients at the Fondation Curie, those surviving five years were, for the most part, patients in whom the carcinomas originated and developed in the upper part of the hypopharynx. With two exceptions, tumours originating in the lower part had not been cured (BACLESSE, 1949). ACKERMAN and REGATO go so far as to consider irradiation to be of no avail in the treatment of post-cricoid carcinomas.

Our results of treatment have been calculated on all treated cases. No case has been eliminated from the material as belonging to an indeterminable group. The observation time is at least two years in all cases. We have been able to trace all our patients.

The results of treatment of all cases, treated 1939—1947, is shown in table V.

Table V.

Results of treatment 1939—1947

Years	No. of cases	Free from signs and symptoms
1	322	95 (30 per cent)
2	322	67 (20 » »)
3	305	51 (17 » »)
5	242	23 (9.5 » »)

It is of special interest to see if our results have improved since we started to use beam direction through fluoroscopy in 1943. Therefore, I have calculated the results separately on the cases treated before and after 1943.

We treated 157 cases, in the years 1939—1942, and 165 cases in 1943—1947. The two groups are composed of similar cases, as the proportion of advanced cases is about the same, as well as the proportion of carcinomas in the lower and upper part of the hypopharynx. Also, the percentage of cases with lymph node metastases in the upper and lower part, in both groups, is the same. Thus, it is possible to compare the results of treatment in the two groups.

AHLBOM (1941) has reported our results in the cases treated up to 1939. He found a five-year cure rate of 7 per cent, the same as in our cases treated 1939—1942, as is shown in table VI. *In the cases treated*

Table VI.

Shows the treatment results in the two groups

Years	Free from signs and symptoms, of 157 cases treated 1939—42	Free from signs and symptoms, of 165 cases treated 1943—47
1.....	26 per cent	32 per cent
2.....	18 » »	24 » »
3.....	15 » »	18 » » (28/148 cases)
5.....	7 » » (11/157 cases)	14 per cent (12/84 cases)

in the years 1943, 1944 and the first half of 1945, the five-year cure rate is 14 per cent.

This improvement of treatment results does not seem to be temporary. On the contrary, there is reason to believe that the permanent results will become better still. *A careful analysis of the cases treated in 1948 and 1949, suggests that a five-year cure rate of about 20 per cent is possible with the present treatment technique.*

Our material, as stated before, is not directly comparable with material from other clinics. We seem to have proportionately more carcinomas, with a prognosis, considered in the literature as very poor.

In table VII, I have, however, compiled some statistics from different countries.

Table VII.

Shows some recent statistics from different countries

Country	No. of cases	Percentage of five-year cures
England (Cade 1949)	44	7
Finland (Sipilä 1949)	172	8
France (Coutard-Baclesse 1949)	425	6
Germany (Glauner 1949)	112	3
Ireland (Douglas 1950)	77	6.5
Norway (Rennæs 1949)	84	7
Sweden (Jacobsson 1950)	84	14

Coutard, to whom due credit must be paid for his pioneer work in the treatment of hypopharyngeal carcinoma, as early as 1935 could report 11 five-year survivals of 89 treated patients (12 per cent). It is doubtful if our results are directly comparable with his, because he does not mention the number of patients *not* treated, and the carcinomas were predominantly situated in the upper part of the hypopharynx. The tumours seem to have been rather well circumscribed and of moderate size, as compared with the great extension in our carcinomas of the lower

part of the hypopharynx. All cases treated by COUTARD are included in the material reported by BACLESSE in 1949 (see table VII). The five-year cure rate in the cases treated by COUTARD and BACLESSE is 6 per cent.

The prognosis for carcinomas in the upper part of the hypopharynx seems to be dependent on the localization of the tumour. ACKERMAN and REGATO consider that carcinomas of the aryteno-epiglottic fold, even though voluminous and accompanied by large lymph node metastases, have a favourable prognosis. Carcinomas of the pyriform fossa, on the other hand, are seldom curable. In our material, there is a rather high percentage of carcinomas of the pyriform fossa: 75 per cent of all carcinomas in the upper part. There also seems to have been a tendency at Radiumhemmet to classify a cancer of doubtful site of origin, as laryngeal carcinoma rather than as hypopharyngeal.

The five-year cure rate in our cases of carcinoma of the upper part of the hypopharynx is about 10 per cent, in spite of the unfavourable material.

Carcinomas of the upper part of the hypopharynx are often referred to as extrinsic larynx carcinomas. Sometimes carcinomas of the pyriform fossa are included in this group, sometimes not. The five-year cure rate in cases which we classify as carcinomas of the upper part of the hypopharynx, seems to vary between 4 and 10 per cent, the best results reported from Finland, Norway, Switzerland (ZUPPINGER) and U. S. A. (MARTIN at Memorial Hospital).

The prognosis for carcinomas of the lower part of the hypopharynx is considered very poor, even if not all authors go as far as ACKERMAN and REGATO, who state that irradiation is of no avail in the treatment of the post-cricoid carcinomas.

The five-year cure rate in our cases of carcinoma of the lower part of the hypopharynx is about 17 per cent in the cases treated 1943—1945. The five-year cure rate was about 5 per cent in the cases treated 1939—1942. Our improvement of treatment results thus has been achieved in the most unfavourable group of hypopharyngeal carcinomas.

Carcinomas of the lower part of the hypopharynx are usually referred to in the literature as post-cricoid carcinomas and carcinomas of the pharyngeal wall. Possibly due to the low rate of cure, few statistics on these tumours have appeared. It has been necessary to make personal inquiries, at some radiotherapeutic clinics, to get materials for comparison. A positive answer was received from the clinics in Dublin (Dr. DOUGLAS), Helsingfors (Dr. SIPILÄ) and Oslo (Dr. RENNÆS), and I am most grateful to these colleagues for the valuable information that they placed at my disposal.

Treatment at a million volts does not seem to have improved the results. WILLIAMS (1948) has reported the results with million-volt

Table VIII.

Shows statistics on the treatment results in cancer of the lower part of the hypopharynx

Country	Material	No. of five-year cures
England (CADE)	11 cases, treated up to 1939 (post-cricoid region and low posterior pharyngeal wall)	0
Finland (SIPILÄ)	42 cases, treated 1936—1944 (lower part of hypopharynx)	0
Ireland (DOUGLAS)	27 cases, treated 1942—1944 (post-cricoid carcinomas)	2
Norway (RENNÆS)	37 cases, treated 1938—1944 (post-cricoid carcinomas)	0
Scotland (MC WHIRTER)	46 cases, treated 1930—1937 (post-cricoid carcinomas)	0
Sweden (JACOBSSON)	56 cases, treated 1943—1945 (lower part of hypopharynx)	10

roentgen therapy at St. Bartholomew's Hospital in London. Of 15 patients with post-cricoid carcinomas, all were dead within two years except one, remaining well four years after treatment.

In this connection, the great palliative effect of the treatment must be emphasized. At present, *one year after treatment, 32 per cent of our cases are free from signs and symptoms of disease, but ten years ago our one-year cure rate was reported as only 16 per cent* (AHLBOM 1941).

Factors influencing the treatment results

A. The tumour dose

It is difficult, according to our experience, to obtain an effective tumour dose with treatment periods longer than four to five weeks. The skin reaction begins after about one month, and the skin is more sensitive to irradiation during this time than otherwise. ZUPPINGER states that a patient may stand a treatment period of more than 40 days better than a shorter one. The number of permanent cures will, however, be lower with the first method, and the patients treated in this way will be more troubled in the future by severe irradiation oedemas.

On the other hand, with a treatment time of less than a month, the risk of complications, such as necrotic disintegration or perichondritis, will increase.

The length of treatment time, the daily dose and the total tumour dose which can be given in any individual case is very much dependent upon the patient's condition, the reaction of the tumour, and the reaction in the tumour bed (the stromal reaction). It is imperative that the irradiation be cautiously administered in advanced cases if there is to be even a small chance of cure. That such a mode of treatment may result in a permanent cure, is shown in Figure 4.

The optimal results, with our treatment method, have been obtained with a tumour dose of 5,700—6,200 r over 26—30 days. A dose of that magnitude

Fig. 4 a.

Fig. 4 b.

Figure 4. Woman, aged 54 on admission, with a typical history of the Plummer-Vinson disease. Carcinoma of hypopharynx and upper part of oesophagus, more than 10 cm long. Lymph node metastases of the neck, about 2.5 × 2.5 cm in size. Roentgen treatment in 1944 with a total tumour dose of about 5,600 r in 27 days. Has been well, and free from signs and symptoms for nearly six years. *A*, Before treatment; *B*, Five years after treatment.

was given in 39 cases treated 1943—1947, and of these, 16 have survived 2 years or more (about 40 per cent).

A permanent cure with a lower tumour dose has been obtained only in rare cases. In two cases, cured for 6 and 9 years respectively, a tumour dose of about 5,400 r over four weeks was given. Biopsy in both cases showed, however, that the tumour ought to be rather radiosensitive. A permanent cure with such a low dose has only been achieved in these two cases in the present material.

A dose of about 6,600 r or more over four weeks may well be considered as above the tissue tolerance dose. Seven patients have been treated 1943—1947, with a dose of 6,600—6,700 r over 29—31 days. All these patients died within one year, due to complications; severe perichondritis in 5 and acute oedema in 2 cases.

One patient seems to have had a tumour dose of a magnitude very near to the tissue tolerance dose. This patient, a male, 36 years old on

admission, had a carcinoma of the extrinsic parts of the larynx, and was treated with a tumour dose of about 6,400 r over 29 days. He is cured and free from symptoms for more than 3 years, but has had two rather severe attacks of acute oedema in connection with colds, in the subsequent course.

B. Metastases

Our experience emphasizes clearly that cases with metastases seldom can be permanently cured, but that we can offer considerable palliation.

The primary tumour, as well as large glandular metastases, may disappear completely, and a 3—4 year survival may be obtained. The patients, however, succumb later to distant metastases.

No single case with metastases, treated 1939—1942, has survived 4 years. The prospects seem brighter, however, in the cases treated in later years. In cases with lymph node metastases, treated 1943—1947, we have 2 cases cured for nearly six years, and another 2 cases healed for nearly five years. In one of the five-year cures, the primary tumour was 10 cm long, and the metastases were only irradiated. In the other five-year cure, the metastases were treated with irradiation and subsequent neck-dissection.

MARTIN and BOWDEN, at Memorial Hospital in New York, have recently (1950) analysed a number of five-year cured cases of cancer of the extrinsic larynx and hypopharyngeal wall, treated 1931—1944. In all cases, from these years, they found only seven with cercival metastases, cured five years or more. There was histologic proof (positive aspiration biopsy) in three of the cases. The total number of cases, treated 1931—1944, is not mentioned.

C. Appearance of a second primary carcinoma

The average frequency of a second primary carcinoma has been reported to be less than 7 per cent (WARREN and GATES, ENGELBRETH-HOLM, WEYDE and others).

In 10 of our 67 cases surviving 2 years or more, a second primary cancer developed (about 14 per cent). None of these tumours developed in the irradiated tissues. *In 9 cases the patient died from the second cancer, free from signs and symptoms of the hypopharyngeal carcinoma.* The second cancer was situated in the digestive tract in 7 cases. The chance of a second primary cancer developing in the digestive tract thus seems to be rather great in patients with hypopharyngeal carcinomas.

Two primary carcinomas were found on admission by ZUPPINGER in about 1 per cent of his cases of cancer in the meso- and hypopharynx. We found the same frequency in our material.

Complications in the subsequent course

A. Acute oedema

Due to unavoidably intense irradiation of the tissues surrounding the tumour, the mucosae of the larynx and hypopharynx become sensitive to infections and irritations, and may react with sudden oedema. The patient must be aware of this risk of complications from the upper air and food passages and told to go to a hospital if he has difficulties with breathing or swallowing. The consulted doctor must also understand the nature of these troubles, and treat the patient accordingly. With proper treatment, with penicillin and sprinkling of the mucosa with a solution of naftylmetylimidazolin-hydrochloride in the concentration 1 : 1,000 and N-cetyl-pyridinii chloride, 2 : 100, we have found that in most cases it is possible to obtain a complete regression of the oedema. Emergency tracheotomy or gastrostomy is seldom necessary.

Oedematous obstruction of the hypopharynx is more frequent in cases with a narrow hypopharynx after treatment. Frequent, carefully managed dilatations are therefore required in these cases.

B. Late reactions, simulating recurrences

After a primary freedom from symptoms, the patient has, in some of our cases, again complained of difficulties with swallowing. These troubles may appear 5—7 months or more after the treatment. Roentgenograms of the hypopharynx reveal radiographic signs which point to the diagnosis of a recurrence. The prevertebral shadow shows increased thickness, and the mucosal lining shows an irregular contour.

Direct endoscopy and biopsy show, however, that the changes are due to oedema and a fibrinous epithelitis, and ought to be explained as a peculiar, late irradiation reaction. The roentgen picture in such cases has been described by WELIN (1948). The sequelae have usually disappeared after 1—2 months.

In 6 of our cases, treated 1945—1947, such »false recurrences» have developed and disappeared without irradiation. All these patients still remain free from symptoms, 4 of them for more than 5 years.

Before 1945, undoubtedly, a number of such »false recurrences» had been treated again with irradiation, resulting in a fatal necrotic disintegration. The radiographic signs, then, were considered as proof of a recurrence, and a biopsy was not taken.

C. Myelodegeneration

In 13 of our cases, treated 1939—1942, symptoms of myelitis of the cervical cord were present, and radiation was considered as the causative

agent. Five of these patients died, in connection with this lesion, 14—15 months after the treatment. Another patient died, 4 years after the treatment, as a result of the myelodegeneration, free from symptoms of the hypopharyngeal carcinoma.

Since we started with beam direction through fluoroscopy and exclusion of the spinal cord from the treatment area, myelodegeneration is no longer a complication to consider. *In the cases treated 1943—1947, not a single case of radiation myelitis has been discovered.*

BODEN (1948) has made a comprehensive study of the radiation myelitis of the spinal cervical cord. In 161 cases, in which the cervical portion of the spinal cord received radiation in significant amount, he found ten cases with symptoms of myelodegeneration. Five of these died as a result of the lesion. The cases had been treated during the years 1942—46. As a result of his analysis he suggested that the cervical cord should not receive more than 3,500 r in seventeen days.

Conclusions

The present investigation has shown that fractionated roentgen treatment is of definite value in the treatment of carcinoma of the hypopharynx. In spite of rather unfavourable material (the tumour more than 5 cm long in nearly half the cases), it has been possible to obtain a five-year cure rate of 14 per cent with our treatment technique. The present results in the cases treated 1948 and 1949, suggest that a five-year cure rate of 20 per cent might be possible.

Improvement in treatment results has been most obvious in cases of carcinoma of the lower part of the hypopharynx. In the literature the prognosis has been considered as extremely poor in these carcinomas. Our present five-year cure rate here is about 17 per cent.

Employing a cross-fire technique with four fields, two on each side of the neck, we have found that it is possible to use rather narrow fields, provided that beam-direction through fluoroscopy is employed. The volume-dose may thus be considered as a minimum.

We have found that it is necessary to administer a tumour dose of about 5,700—6,000 r in about four weeks. A permanent cure, with a lower dose has been obtained in only a few cases. Doses of 6,600 r or more in a month have resulted in fatal complications in all cases.

It must be emphasized that the treatment in the individual case must be carried out with proper consideration of the patient's general condition and the extension and mode of growth of the tumour. The treatment must be modified according to the reaction of the tumour and the surrounding tissues (the stromal reaction). A superficially growing, papillomatous tumour can often be rather intensively irradiated

without subsequent complications, whereas cautious treatment is advised in case of an infiltrating tumour with little stroma, especially if the tumour is situated near cartilage or bone.

Due to the unavoidably intense irradiation of the tissues surrounding the tumour, the mucosae of the larynx and hypopharynx become sensitive to infections and irritations. Acute oedema in the subsequent course is a dangerous complication and may, without proper treatment, lead to sudden death. The patient must be told to go immediately to a hospital if he has stridor or difficulties with swallowing. Emergency tracheotomy may be necessary, but in most cases the oedema disappears with proper treatment with penicillin and sprinkling of the mucosa with a solution of naftylmetylimidazolin-hydrochloride and N-cetylpyridinii chloride.

In some cases, where primary freedom from symptoms has been achieved, symptoms may again develop simulating a recurrence. The roentgen examination may show changes which point to the diagnosis of a recurrence, as increased thickness of the prevertebral shadow and an irregular contour of the mucosal lining. Direct endoscopy and biopsy will, however, reveal that the symptoms are due to oedema and an epithelitis, and ought to be explained as a peculiar, late irradiation reaction. The changes usually have disappeared again after 1—2 months. It is therefore imperative that irradiation of a recurrence must not be given, before a biopsy has confirmed the diagnosis.

The formerly much dreaded complication of myelodegeneration of the cervical cord has not occurred since we began to employ beam-direction through fluoroscopy, with exclusion of the spinal cord from the treatment area.

Further improvement of the results cannot be obtained only by more accurate treatment technique; it is of utmost importance that we get better material to treat. At present about 1/3 of the patients are in such an advanced stage of disease on admission that it is impossible to go through with the treatment.

Teaching of doctors and nurses who are in close contact with the population, about the symptoms of early hypopharyngeal cancer, is very important.

The connection of sideropenia and cancer of the hypopharynx, as well as carcinomas in other parts of the digestive tract (Ahlbom and Jacobsson), makes it probable that the prevention of these carcinomas in a considerable proportion of individuals becomes a possibility. Patients, with sideropenia or the Plummer-Vinson syndrome, must be kept on regular controls. An adequate diet, rich in iron and vitamines, especially the vitamine B complex (fresh meat, cheese and vegetables), ought

to be provided for the patients. It is probable that the cause of sideropenia is a hereditary insufficiency to take up from the food the necessary amount of iron and/or substances regulating the serum iron.

SUMMARY

An analysis is made of the cases of hypopharyngeal carcinoma treated at Radiumhemmet 1939—1947. The present five-year cure rate is about 14 per cent. The present method of roentgen treatment, with beam direction through fluoroscopy, is described. The influence of the tumour dose on the treatment results and the various complications after the treatment are discussed.

ZUSAMMENFASSUNG

Es wird eine Einteilung der Fälle von Hypopharynx-Carcinom vorgenommen, die 1939—1947 in Radiumhemmet behandelt wurden. Die gegenwärtige Ziffer der Fünf-Jahres-Heilung beträgt ungefähr 14 %. Die jetzt gültige Methode der Röntgenbehandlung wird beschrieben, bei der die Strahlenrichtung vermittels Durchleuchtung eingestellt wird. Der Einfluss der Tumor-Dosis auf die Behandlungsergebnisse und die verschiedenartigen Komplikationen nach der Behandlung werden besprochen.

RÉSUMÉ

Analyse des cas de cancer de l'hypopharynx traités au Radiumhem de 1939 à 1947. La proportion actuelle des guérisons après 5 ans est d'environ 14 pour cent. Description de la méthode radiothérapique présentement utilisée, avec son réglage sous radioscopie de la direction du rayon central. La discussion porte sur l'influence que la dose tumorale exerce sur le résultat thérapeutique et sur les diverses complications succédant au traitement.

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FROM PHILIPS ROENTGEN RAY LABORATORIES, EINDHOVEN, HOLLAND

THE RELATION BETWEEN TENSION AND EXPOSURE TIMES IN RADIOGRAPHY[1]

by

A. Bierman and *W. Hondius Boldingh*

It is a remarkable fact that although roentgen rays have been employed in medical practice for more than half a century, and excellent radiographic results have been obtained for many years, there is as yet still no generally accepted formula for the relationship between kV and mAs, for a requisite amount of photographic density in a radiograph.

Elaborate exposure experiments, covering several regions of the body, thorax, stomach, pelvis, etc. and employing widely varying tensions have shown that, where the exposures were correct in terms of density, the resultant radiographs were almost identical in appearance. It was, in fact, extremely difficult to see any difference between these films (Dr. v. d. PLAATS, Miss VAN DIJK 1941). At that time the need was already felt for a mathematical expression giving the relationship between tension and mAs (COOLSMA).

From time to time various manufacturers have produced slide rules for the purpose of determining the various values for radiographic exposures. One of the basic essentials of such slide rules must obviously be the above mentioned relationship between kV and mAs. Moreover some work has been done on this subject by OOSTERKAMP (Thesis, Delft 1939), but in general there has been no uniformity in the results and an established formula has so far not been evolved.

The need of producing such a formula has led us to investigate this subject more systematically because of the importance of the conclusions which can be derived, together with their practical applications.

It has been found that, with all other factors (object, focus-film distance, film and screen material, etc.) remaining constant, a slight variation in kV, for example 1 %, can be compensated by an mAs variation of 4 % to 6 %. This holds good for the whole range of tensions between

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50 and 100 kV. (Throughout this article the term kV implies the peak value.)

Translated into a mathematical formula, this may be expressed as follows:

$$\text{For constant blackening: } \text{mAs} \times (\text{kV})^p = \text{Constant}$$

where p is an exponent between 4 and 6.

This corresponds for example with the experimental fact that by doubling the tension the mAs-value can be reduced to about 1/30.

The object of our investigation has been to determine experimentally the value of the exponent p under practical conditions employing various object thicknesses, with and without bucky grids and with miniature radiographs (with camera) as well as full size radiographs. As already mentioned above, the general conclusion has been that within the normal range of diagnostic tensions, 50 to 100 kV, the value of p is between 4 and 6. It will be shown that the average value, *i. e.* 5, satisfies all practical requirements.

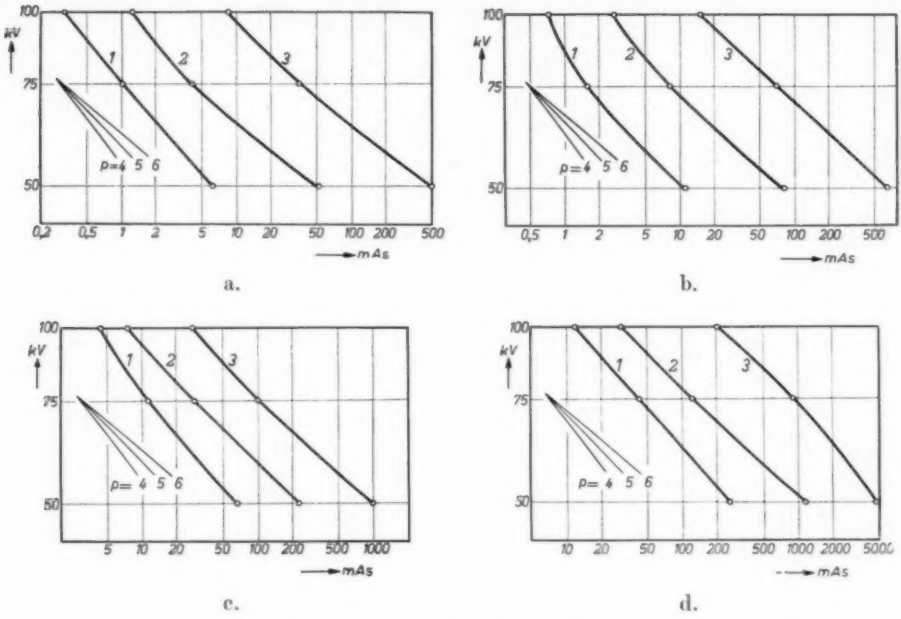
In order to determine the value of p in various circumstances, we have carried out a number of measurements with bakelite phantoms. Bakelite has been found to be a good substitute for the human body, as far as absorption, dispersion, etc. are concerned. (See the article of Burger, Acta Radiologica, Vol. XXXI, 1949, p. 195.)

Using three thicknesses of phantoms, viz. 5, 9 and 15 cm, exposures were made with 50, 75 and 100 kV. By variation of the exposure times, the quantity of mAs necessary to produce a certain degree of blackening, has been determined in all these cases. This mAs value has been plotted against the tension for a blackening value of 1.0. Since logarithmic scales have been employed for these mAs — kV diagrams, the slope of a curve gives the corresponding value of p. If the value of p had been constant throughout the whole range between 50 and 100 kV, then a straight line would have been obtained. This, however, was generally not the case, but the curvature was always so slight that the *average slope* of each curve gives a sufficiently reliable value for p.

The exposures were all made with a four-valve apparatus. There is no reason to assume that other wave-forms will yield different results.

The diagrams, a, b, c and d show the curves obtained from:

(a) Full size radiographs, without grid, Gevaert »CURIX» film, »Ampli» intensifying screens.
(b) Same as (a), but with a grid.
(c) Miniature radiographs, without grid, made with Philips Mirror Camera on 45 mm Gevaert »SCOPIX G» film, in combination with a Levy-West »Mark 48» fluorescent screen.
(d) Same as (c), but with a grid.



In each diagram the curves 1, 2 and 3 refer respectively to 5 cm, 9 cm and 15 cm thickness of the bakelite phantom.

In the following list are tabulated the values of p derived from the diagrams.

Thickness of phantom			5 cm	9 cm	15 cm
Full size radiographs.	a	p without grid	4.3	5.4	5.9
	b	p with grid	4.0	4.9	5.4
Reduced radiographs.	c	p without grid	3.9	4.9	5.2
	d	p with grid	4.4	5.2	4.6

The values in this table show that p generally increases more or less with the thickness of the object. The average of all the 12 values listed is $p = 4.8$. However, in view of the divergence of the results, it is obviously practical to take the value as a round number. Therefore the conclusion of our measurements can best be expressed as follows:

For constant density: $(kV)^5 \times mAs = Constant$

Although this table refers to only two film and screen combinations, other experiments with bakelite phantoms employing a great many

film and screen combinations have confirmed that exposures based upon $p = 5$, fulfil all practical requirements. (These experiments were carried out to investigate the qualities of various films and screens.)

From the above table it is easily seen that the mean deviation of p is only 0.5 when taking $p = 5$. This deviation is quite admissable in practice. When, for example, the tension is varied by a factor of 2, the mean exposure deviation will be $2^{0.5} = 1.4$. However, a tension variation for any given object will never be as great as this in actual practice. Even a factor of 1.5 seldom occurs and in this case the mean deviation is only $1.5^{0.5}$, which is a factor of 1.2. This is hardly perceptible.

Even a deviation in p as large as 1.0 is of little practical significance, since the other sources of error (*e. g.* due to the unverifiable degree of absorption in the object) are generally more important.

From the above it will be seen that in diagnostic radiography the value $p = 5$ can be employed with the assurance that the deviations of this magnitude have no appreciable significance.

Finally we would draw attention to the fact that the use of the mAs number, in radiographic calculations does not meet with any objections in practice. This is in spite of the wellknown fact that because the reciprocity law does not hold, the use of such numbers is not quite correct (Schwarzschild exponent). The magnitude of the errors thereby introduced, being similar to any which might be obtained by the use of a constant p value, fully justifies the employment of the latter.

Various applications of this rule will be dealt with in a future publication. Here we will conclude only by giving a simple example as it may occur in actual practice.

»How much must the tension be increased in order to obtain the same degree of blackening, when using only half the quantity of mAs?»

Since $(kV)^5 \times mAs$ must remain unchanged, a doubling of $(kV)^5$ is necessary in order to compensate for the halving of mAs. The tension, therefore, must be multiplied by a factor $2^{1/5} = 1.15$. In other words: for half the mAs value, 15 % more tension is required.

SUMMARY

Experiments, carried out under widely varying conditions, have proved that the density of a radiograph remains practically constant when varying kV and mAs in such a way, that the value of the product $(kV)^5 \times mAs$ is kept constant. Application of this rule does not give intolerable deviations in the whole field of diagnostics.

ZUSAMMENFASSUNG

Versuche ausgeführt unter sehr verschiedenen Umständen haben gezeigt, dass die Schwärzung einer Röntgenaufnahme praktisch konstant bleibt wenn man kV und mAs

derartig ändert, dass das Produkt $(kV)^5 \times MAs$ konstant gehalten wird. Anwendung dieser Regel gibt keine unzulässige Abweichungen im ganzen diagnostischen Gebiet.

RÉSUMÉ

Des essais, faits sous des conditions très différentes, ont montré que le noircissement d'une radiographie reste pratiquement constant, quand on varie le kilovoltage et les mAs de telle manière que la valeur du produit $(kV)^5 \times mAs$ ne change pas. Application de cette règle ne donne pas de déviations intolérables dans tout le domaine diagnostique.

FROM THE RADIOLOGICAL CLINIC (DIRECTOR: PROFESSOR CARL KREBS) OF THE UNIVERSITY OF AARHUS, DENMARK

CALCULUS-CONTAINING URETHRAL DIVERTICULUM IN A WOMAN[1]

Report of a Case

by

Olaf Brøbeck

While urethral calculi are comparatively frequent in men, they are of rare occurrence in women. Calculus formation may be due to a number of different causes:

I. Endogenous Origin

a. *Retention of calculi descending from the upper urinary tract.* (Secondary calculi, rare.) Calculi of such origin are not uncommonly multiple (BIBUS, 1937); b. *Calculus formation in urethral diverticula.*

According to JOHNSON (1938) urethral diverticula may arise in the following ways: *Acquired:* 1. Trauma of childbirth; 2. Infection of the urethral glands, with sealing off of the opening to the urethra, formation of an abscess and re-establishment of communication; 3. Instrumentation; 4. Secondary to urethral stricture; 5. Secondary to urethral stone. *Congenital:* 1. Gartner's duct; 2. Cysts formed from faulty union of primal folds; 3. Cell rests; 4. Wolffian duct; 5. Vaginal cysts.

II. Exogenous Origin

Incrustation of retained foreign bodies inserted into the urethra, such as hair-pins (CHATELIN, 1900; GAROFOLO, 1929).

Diverticula of the female urethra are almost invariably situated in the urethrovaginal septum, usually in the middle third. They communicate by a narrow, often valvelike, opening with the urethra. The contents of the diverticulum generally consist of urine or pus.

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Urethral calculi are most frequently formed in diverticula (primary calculi). In 1944 HERMAN and GREENE mentioned 63 cases of diverticulum, 11 of which (17 per cent) were complicated with calculi.

In 1934 SHIVERS and COONEY found 22 cases of urethral calculus in a review of the literature and reported one case of their own.

In 1939 GASTON and FERRUCI mentioned 33 cases and reported one of their own; in 1943 HIGGINS and ROEN stated that 39 cases were on record; finally, in 1948 ZIDE estimated the number of cases so far reported at about 40.

For several obvious reasons secondary calculi in the female urethra are of rare occurrence, chiefly because vesical calculi *per se* are uncommon in females, and even a comparatively large stone may pass naturally from the bladder because the female urethra is short, straight, and easily dilatable. Only a few authors consider secondary calculus formation in the urethra to be more common than the primary variety (KOCH, 1927; SHIVERS and COONEY, 1934).

A difference of opinion exists as to the origin of the diverticula. JOHNSON (1938) believes that most frequently they are congenital. He bases this opinion on the finding of a cyst in the anterior vaginal wall in a newborn girl with urinary retention due to pressure on the urethra; this cyst might — so JOHNSON says — become a diverticulum if a communication with the urethra developed. Only a few cases of diverticulum have been found in young nulliparae and children.

Most other authors (ZIDE, 1948; MENVILLE and MITCHELL, 1944; HERMAN and GREENE, 1944, and others) regard trauma and infections as the principal causative factors. During labour, pressure of the child's head against the symphysis pubis is said to cause a crushing of the muscularis of the urethra, permitting a subsequent hernial protrusion of the mucosa and submucosa (SHIVERS and COONEY, 1934). Catheterization and infection during labour must be supposed to be of importance. This supposition is in good agreement with the fact that diverticula (with or without calculi) are most frequent in women over 40 who have borne one or more children.

The periurethral glands have been subjected to a close study; while JOHNSON bases his hypothesis of the congenital origin of the diverticula on studies made by CABOT and SHOEMAKER (1936), who did not find glands in the posterior half of the female urethra, others, *e. g.* HUFFMAN (1948), have demonstrated the presence of glandular elements around the entire length of the urethra (in addition to Skene's para-urethral ducts, which run parallel to the urethra, sometimes right up to the vicinity of the bladder neck, and may contain tubular glands, in which calculus formation *may* occur (HERZENBERG, 1933)).

Inflammatory occlusion of a glandular duct and subsequent rupture into the urethral lumen may be the starting-point of a pouch or a diverticulum in the urethra. Local urinary stasis, infection, and precipitation of urinary salts may result in calculus formation (HIGGINS and ROEN, 1943).

Symptoms

The symptoms of urethral diverticulum (with or without calculus) depend on the size of the diverticulum and the severity of infection. Although the condition may sometimes be symptomless, it is usually accompanied by intermittent attacks of dysuria, nocturia, pyuria, and occasionally by hematuria, a bearing-down sensation, burning in the vulva, and dyspareunia. A pathognomonic symptom of the presence of a diverticulum is a palpable mass in the anterior vaginal wall, which empties on pressure.

Local Examination

A smooth, rounded and fluctuating mass may be seen and felt in the anterior vaginal wall just inside the introitus. It ranges from the size of a bean to that of a hen's egg; if the diverticulum contains calculi, it will be hard to the touch, and palpation may produce crepitation. The hard mass may give rise to suspicion of a malignant tumour (one of HERMAN and GREENE's cases was referred to them on suspicion of malignancy).

Urethroscopy and *roentgenography*, especially a cystogram with a urethral catheter in place, will confirm the diagnosis.

Treatment

The treatment of choice is radical excision of the diverticulum containing the calculus or calculi. This procedure generally results in a complete cure.

Own Case

Rec. No. 1400/40. A woman, born September 9, 1885, was admitted to this clinic for cancer of the cervix uteri, grade III, on August 16, 1940. She gave a history of previous good health, except for an appendectomy in 1916. She had had four normal deliveries, but no abortions. She had passed through the menopause at 47 without any discomforts.

For several years she had had a slight non-bloody vaginal discharge, which had not caused any discomfort. During the last six months there had been vaginal bleedings, at first at intervals of 2—3 weeks, lately several times a week. No pain or tenderness.

She had no urinary complaints; the bowel movements were normal; no fatigue or loss in weight.

Physical Examination: Slight anemia of the mucosae; excellent nutritional condition. Except for the anemia the physical examination was uncontributory.

Fig. 1.

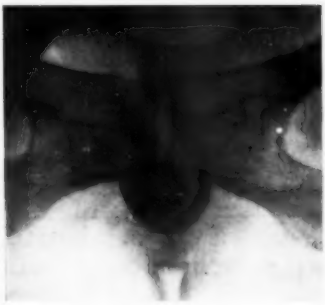

Fig. 2.

Fig. 1. Showing the nutmeg-sized bulging in the anterior vaginal wall just inside the introitus.

Fig. 2. Roentgenogram of the infrapubic region, showing a rounded calculus shadow below the symphysis in the midline; size $2^1/_2 \times 3$ cm.

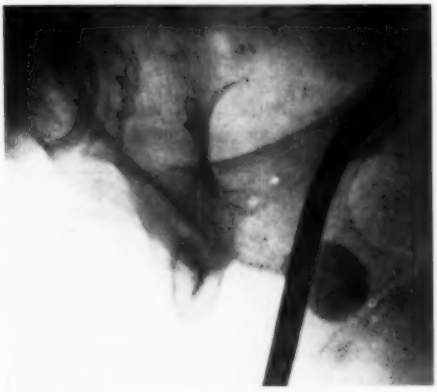

Fig. 3 a. Oblique view.

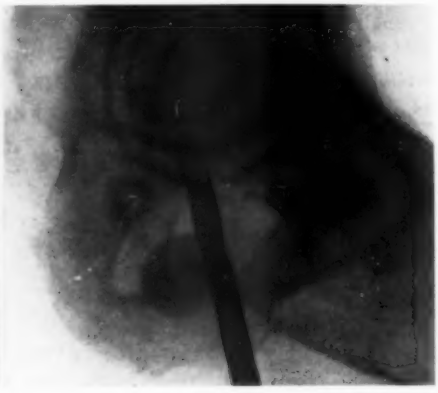

Fig. 3 b. Lateral view.

With the urethral catheter in place the calculus is seen behind the lower portion of the urethra.

Gynecologic Examination: Cystoscopy: Slight diffuse injection of the bladder wall, otherwise nothing abnormal. A large, crateriform ulceration on the uterine cervix and infiltrations of both parametria. *Diagnosis:* Cancer of the cervix uteri, grade III.

Laboratory Findings:

S. R.: 61 mm. Hb.: 74 %. Red blood cells: 3,650,000. White blood cells: 5,850. The differential count was normal.

Roentgenography of the lungs: Nothing abnormal. *Roentgenography of the pelvis:* No osseous changes. No signs of calculi in the infrapubic region.

Catheterized urine was negative for albumin, positive for leukocytes and organisms.

The patient received roentgen and radium treatment and reported repeatedly for follow-up examination. There was no evidence of recurrence of cervical cancer. On one occasion a slight rectal bleeding had developed. She had no complaints from the urinary tract.

At a follow-up examination on January 27, 1944, a firm nutmeg-sized lump was felt in the urethrovaginal septum just inside the introitus. There was no ulceration of the vaginal mucosa. At subsequent follow-up examinations (at intervals ranging from six to twelve months) the intumescence was unchanged in size and was supposed to be a calcified cyst.

On January 30, 1950, the patient was referred to this clinic from another hospital with a diagnosis of vaginal metastases from her cervical cancer.

Gynecologic Examination: As before a nutmeg-sized hard, firm lump in the anterior vaginal wall was found (Fig. 1); no signs of recurrence of the cancer. *Bladder catheterization* (Professor Krebs): As a scratching sensation was felt when the catheter was passed beyond the tumour, the presence of a calculus was suspected.

A roentgenogram of the vesical region (Fig. 2) showed a rounded, calculus-like shadow, $2^1/_2 \times 3$ cm, in the midline just below the lower margin of the symphysis, and roentgenograms with a metal catheter in the urethra (Figs. 3 a and b) revealed that the calculus was situated behind the lower portion of the urethra.

Comments

A roentgenogram of the infrapubic region from 1940 showed no calculus shadow. Thus the calculus must have developed after that time.

There have not, at any time, been symptoms of calculi in the urinary tract. It must therefore be regarded as likely that it was a primary urethral calculus which had developed in a diverticulum. The roentgen and radium therapy used in 1940 consisted of a standard course of treatment and was not attended with any difficulties. It is difficult to say whether the treatment has been concerned in the production of the presumed diverticulum.

This case differs from most other cases previously reported in that the calculus has not given any symptoms, and repeated examinations of the urine have not shown any signs of infection of the urinary tract, except at the first examination. Since the calculus does not cause any discomforts to the patient, she has refused operation.

SUMMARY

In a 64-year-old woman, who was treated for cancer of the cervix uteri, grade III, in 1940, a calculus subsequently developed in the lower portion of the urethra — in the urethrovaginal septum — presumably in a diverticulum. On examination the calculus measured $2^1/_2 \times 3$ cm (on the roentgenogram).

As the calculus gave no symptoms the patient refused operation. Owing to the presence of the hard tumour in the vaginal wall the patient was referred to the radiological clinic on the suspicion of vaginal metastases from her previous cervical cancer.

ZUSAMMENFASSUNG

Bei einer 64-jährigen Frau, die 1940 wegen Gebärmutterhals-Krebses III. Grades behandelt wurde, entwickelte sich in der Folgezeit eine Steinbildung in dem unteren Abschnitt der Urethra — in dem Septum urethrovaginale — vermutlich in einem Divertikel. Bei der Untersuchung mass der Stein $2^1/_2 \times 3$ cm (auf dem Röntgenbild).

Da das Konkrement keine Symptome hervorrief, lehnte die Patientin die Operation ab. Infolge des Vorhandenseins des harten Tumors in der Vaginalwand wurde die Patientin der radiologischen Klinik überwiesen unter dem Verdacht einer Metastase von dem früher bestandenen Carcinom.

RÉSUMÉ

Chez une femme de 64 ans, traitée pour cancer du col de l'utérus du III^e degré, en 1940, il se développa par la suite un calcul dans la partie inférieure de l'urèthre — dans la cloison uréthro-vaginale — probablement au sein d'un diverticule. A l'examen, le calcul mesurait $2^1/_2$ sur 3 cm (sur la radiographie).

Comme le calcul ne donnait pas de symptômes la malade se refusa à l'opération. A cause de la présence de cette tumeur dure la patiente avait été envoyée à la Clinique Radiologique parce qu'on suspectait des métastases vaginales de son ancien cancer.

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THE PROPERTIES OF FINE-GRAINED PHOTOGRAPHIC EMULSIONS USED FOR MICRORADIOGRAPHY[1]

by

A. Engström and *B. Lindström*

Introduction

The increasing use of quantitative microradiographic procedures for chemical analyses in *e. g.* metallurgy, biology and medicine necessitates knowledge of the photographic response of fine-grained film emulsions to extremely soft roentgen rays. Most investigations of the photographic action of roentgen rays have been performed with hard roentgen rays used for different diagnostic purposes and on coarse-grained film emulsions. In 1947 a short communication was published by ENGSTRÖM and LINDSTRÖM on the photographic action of roentgen rays of wavelengths 2.5 to 25 Å in *Agfa Printon* and *Ilford high resolution* plates.

There are some scattered investigations on extremely fine-grained emulsions blackened by light or electrons. Thus the properties of very fine-grained plates, such as *Lippmann* plates, »Mikratplatten» and »Frieserplatten» were investigated for light and electrons by KOPP and MÖLLERSTEDT 1946. They determined the sensitivity, resolving power and the shape of the density curve.

The resolving power (granularity) is the most important property of the photographic plate used for microradiography. At present the *Lippmann* film, *Eastman Kodak* Spectroscopic Plates 548—0 and 649 are those plates, commercially available, with the best resolution and suitable for microradiography.

Material

The following types of fine-grained emulsions have been tested for use in microradiography: *Lippmann* emulsion on celluloid base, manu-

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factured by *Gevaert*, Antwerp, and *Eastman Kodak* Spectroscopic Plates, types 548—0 and 649.

The coarse-grained emulsions used for comparison were *Agfa Printon* film and *Kodak* No. Screen roentgen film.

In order to compare the different emulsions they were developed in the same developer under constant temperature + 20° C. For *Eastman Kodak* Spectroscopic Plates 548—0 and 649 *Kodak* developer D 19 or D 8 (high contrast) are recommended. The developer used in the experiments, however, had the following composition:

Metol	4 g
Sodium sulf. cryst.	130 g
Hydroquinone	10 g
Sodium carb. cryst.	110 g
Potassium bromide	5 g
Water to	1,000 ml

The developing time was 5 minutes. The plates were then rapidly washed and fixed for 5 minutes in ordinary hypofixative. They were then washed for 30 minutes and dried in a dustfree space.

Technique

The *Machlett* roentgen ray tube, type AEG 50 T, was used as roentgen ray source in most of the experiments. The voltage across the tube was 4.50 kV D. C., well smoothed. Thus the radiation had a short wavelength limit of 2.74 Å and the inherent filtration in the tube window is about 1 mm beryllium, absorbing practically all the radiation above 4 Å. The shape of the roentgen spectrum can be seen from figure 1. The high voltage was carefully stabilized. The distance between film and target was about 50 mm. The exposure times for the most insensitive emulsions amounted up to 1 hour.

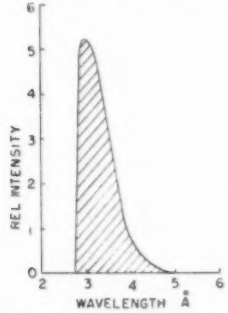

Fig. 1. Shape of the roentgen spectrum used for the experiments.

In case of roentgen rays the Schwarzschild exponent is 1. When recording the density curves a wedge system, made of nitrocellulose foils, was photographed with roentgen rays on the film. Also a series of different long exposures were taken on one and the same film with constant roentgen ray output of the tube. After development, fixation, washing and drying the density of the plates was determined by photometry. Two types of instruments were used, a selfrecording photometer, employing a termocouple as light sensitive part and with a slit width of 0.2 × 0.4 mm and one by which

points down to 0.2 mm in diameter could be measured. The latter type of photometer has a photomultiplier tube for light reception and has been described by ENGSTRÖM, WEGSTEDT and WELIN 1948. The step wedge for absorption of roentgen rays was checked by measuring the roentgen ray absorption in each step iontometrically, and the roentgen ray beam was enough filtered in the tube window to give a linear absorption in the foils (cf. fig. 2).

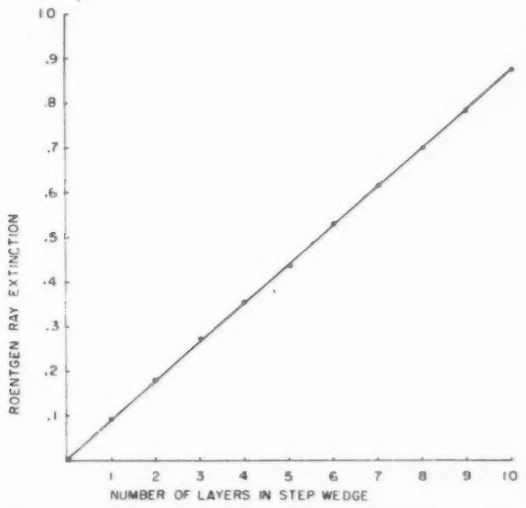

Fig. 2. The absorption of 4.5 kV roentgen rays in the foils used for the step wedge.

The resolving power was tested by exposing different types of nets or gratings on the film emulsion. Biological objects were microradiographed when determining the ultimate limit of resolving power, and the technique developed by ENGSTRÖM 1946—49 was employed. The shrinkage effects of the photographic emulsions were estimated by taking a contact picture of either a brass plate with small holes or of a thin steel wire with crosses at the ends and of certain length. In the first experiment shrinkage could be measured in a not blackened emulsion and in the second case in emulsions blackened to different extent.

Enlargements of the microradiograms were obtained by ordinary photomicrography. In order to get good images the small microradiograms were placed on an object glass with the emulsion side upwards and a cover slip was pressed against the emulsion. *Gevaert Replica* Plates were used for the photomicrography.

The Shape of the Density Curve

Fig. 3 shows the density versus incident roentgen ray energy in a logarithmic scale for *Lippmann* emulsion and *Eastman Kodak* Spectro-

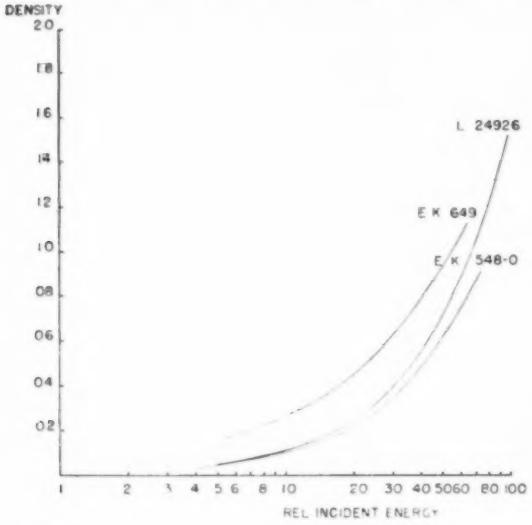

Fig. 3. Density curves for different fine-grained film emulsions. Fog is subtracted.

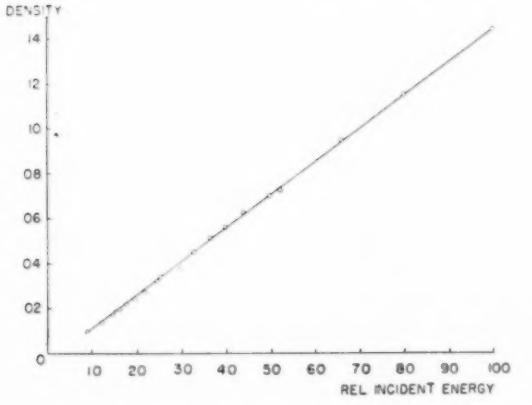

Fig. 4. Density curve for Lippmann emulsion (24,926).

scopic Plates 548—0 and 649. Higher densities than up to 1.5 have not been investigated. The figure shows that the *Lippmann* emulsion is the steepest one of the three when density exceeds c:a 0.5. Moreover, for Spectroscopic Plate 649, *Lippmann* emulsion and Spectroscopic Plate

548—0 the ratio between the roentgen ray energies, required to produce a density of 0.5, is about 22 : 37 : 41.

As the *Lippmann* emulsion has the widest use for microradiography at present, the relationship between density and incident energy was investigated also at relatively low energies. Fig. 4 shows some results obtained with different *Lippmann* emulsions. The fog is subtracted. It is interesting to note that there is a straight line relationship between density and incident energy up to a relatively high density. This fact can be used for quantitative purposes as the ratio of two densities also is the ratio of the corresponding incident roentgen ray energies on the film.

For softer roentgen rays than those used in the experiment related above, the straight portion of the curve becomes shorter. In some investigations the density curve did not pass through the origin of the coordinates but cut the x-axis at a small distance from origo. If this finding depends on an experimental error or some sort of a lag in the emulsion is not yet clear.

Sensitivity

The sensitivity of the different emulsions was investigated with 4.50 kV roentgen rays and at a density of 0.5. The values obtained are given in table I.

Table I

Film emulsion	Relative sensitivity
Eastman Kodak No. Screen	1
Agfa Printon	1/4
Lippmann	1/10,000
Eastman Kodak 548—0	1/10,000
Eastman Kodak 649	1/5,000

The table shows that very fine-grained film emulsions are about 5,000—10,000 times less sensitive than ordinary roentgen ray film. The sensitivity of the emulsion depends besides of grain size also on the thickness of the emulsion coating. Roentgen rays of a wavelength of 3 Å have a half value layer thickness in silver bromide of about 1 μ and in an ordinary emulsion the same value is about 5 to 10 μ. Therefore an emulsion about 5 μ thick is much more sensitive than one which is 1 μ thick with the same grain size.

Resolving Power and Granularity

The resolving power of the emulsions can be seen from table II. According to that the best emulsion should be *Lippmann* and Spectroscopic Plate 649.

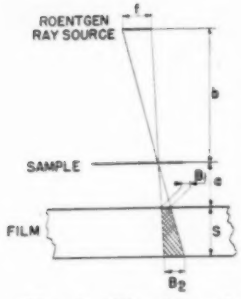

Fig. 5. Blurring of image in microradiography.

When testing the resolving power the geometrical conditions at the experiments play an important rôle. The blurring of a point in a thin sample (cf. fig. 5) at a distance a from the film emulsion and at a distance b from the roentgen ray source is

$$B_1 = \frac{f \cdot a}{b},$$

where f is the magnitude of the focal spot. If the film emulsion has the thickness s and the roentgen rays penerate the whole emulsion the blurring is

$$B_2 = \frac{f(a+s)}{b}.$$

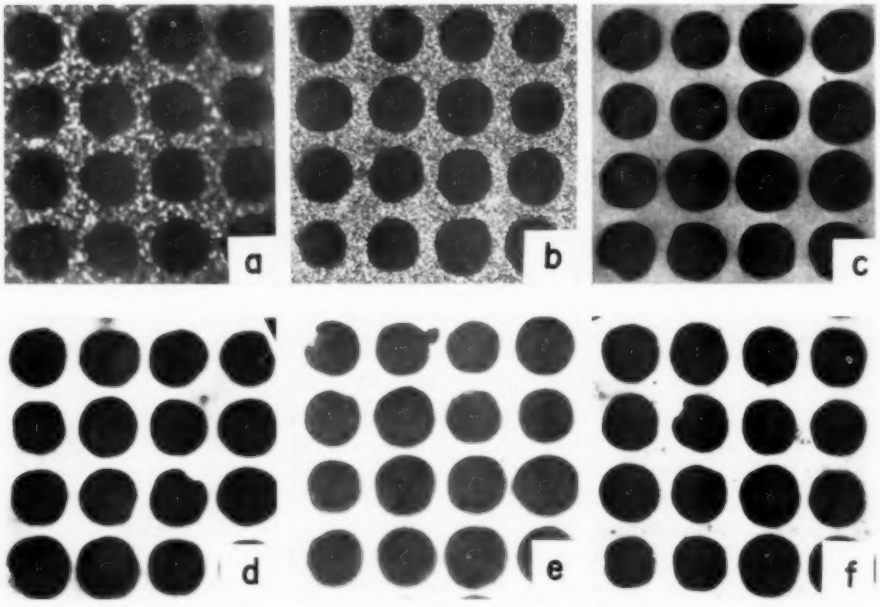

Fig. 6. Resolving power of different film emulsions. An electron microscope screen photographed with 4.50 kV roentgen rays.

a. Eastman Kodak No. Screen Roentgen film.
b. Agfa Printon Film.
c. Eastman Kodak Spectroscopic Plate 649.
d. Eastman Kodak Spectroscopic Plate 548—0.
e. Lippmann emulsion nr. 24,926 (Gevaert).
f. Lippmann emulsion nr. 75,260—2 LD (Gevaert).
Magnification in all cases 80×.

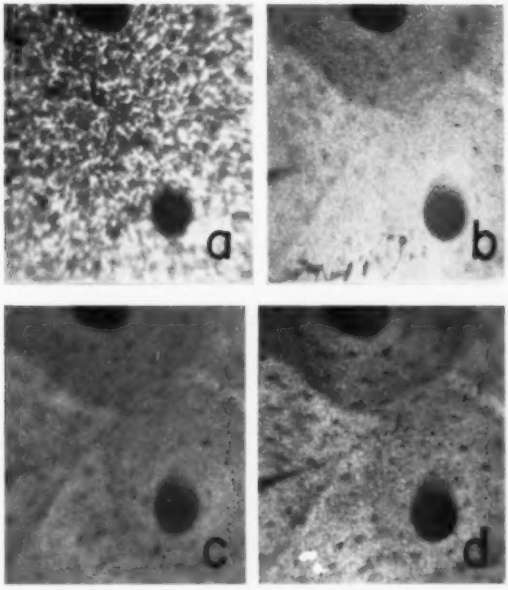

Fig. 7. Photomicrograph of a microradiogram of a ground bone specimen.

a. Agfa Printon Film.
b. Lippmann emulsion number 75,260—2 NE.
c. Eastman Kodak 649.
d. Eastman Kodak 548—0.

The conditions for microradiography used at the authors' laboratory are when best: $f = 5$ mm, $b = 50$ mm and $a =$ about 5 μ, which gives a blurring of 0.5 μ. If the film emulsion has the thickness 25 μ the blurring is 3 μ. It is therefore important to have very thin emulsions for microradiography. The *Lippmann* film had the thinnest coating of the film emulsions used.

Table II

Film emulsion	Resolving power (lines/mm)
Kodak No. Screen Roentgen Film	$\sim$ 10
Agfa Printon	$\sim$ 50
Ilford High Resolution	$\sim$ 75—100
Eastman Kodak Spectroscopic Plate 548—0	$\sim$ 500
Eastman Kodak Spectroscopic Plate 649	$\sim$ 1,000
Lippmann Film	$>$ 1,000

The resolving power of the different emulsions at low power can be seen from fig. 6, where an electron microscope screen is photographed with roentgen rays. The screen was in close contact with the film. Fig. 7 shows enlargements of a ground bone specimen, 20 μ thick, taken on different film emulsions. Fig. 8 shows a high power microradiogram of a striated muscle fibre and fig. 9 a microradiogram of a section of bone.

Fig. 8. High power microradiograph of a section of striated muscle fibres. The different cross bands can be clearly seen. Lippmann emulsion.

The grain size of *Lippmann* emulsion is submicroscopic, and electron microscope investigations give a value of the grain diameter of 10 to 50 mμ. The grain size is different for different emulsion numbers and is affected by heat, storage etc. In enlargements of microradiograms associations of grains, visible in the light microscope, can be seen.

Shrinkage Effects

The shrinkage effects were examined both in maximally blackened and in un-blackened emulsions developed, fixed etc. in standard way. In all emulsions used the concentration or elongation of the emulsion was less than 0.1 %.

Development Artefacts

Development defects might occur on the border between a strongly and a weekly exposed area in a photographic emulsion (cf. MEES). They depend upon that the strongly exposed area »draws» developer from the

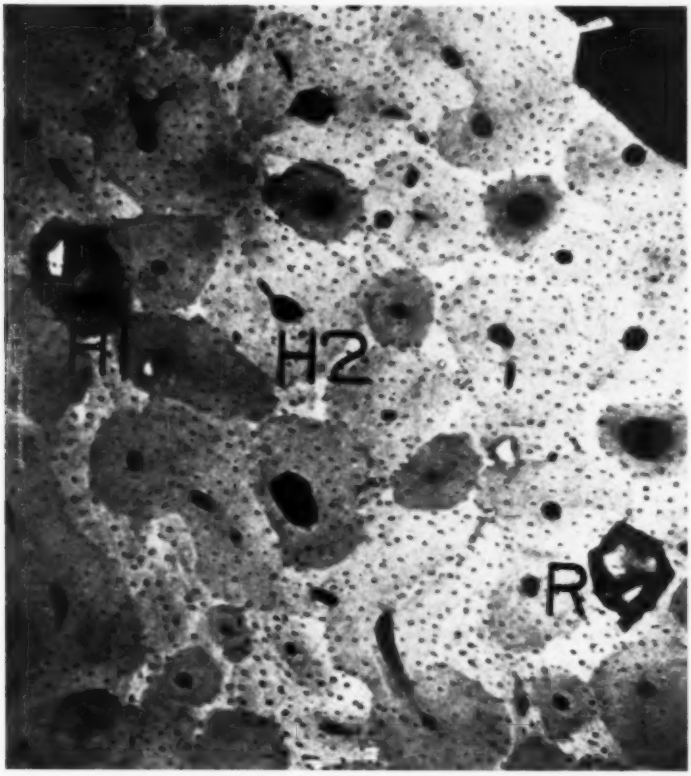

Fig. 9. Photomicrograph of a microradiogram of a ground bone specimen. Note the difference in calcification between the Haversian systems.
H 1 a young, growing Haversian system.
H 2 an old one.
R is a resorption cavity.

weekly exposed part. A small, exposed area may therefore be more dense than a large one even if the incident roentgen ray energy per unit area is the same.

Lippmann film was tested for the *Eberhard* effect with a density up to 1. The smallest exposed area had a diameter of about 0.5 mm and the largest one was 5 mm in diameter. The differences in density between the small and large area did not exceed the variations of the film emulsions. This result was expected as the *Eberhard* effect diminishes with thinner emulsion layers. The effect is very marked in strongly exposed films with thick emulsion layers.

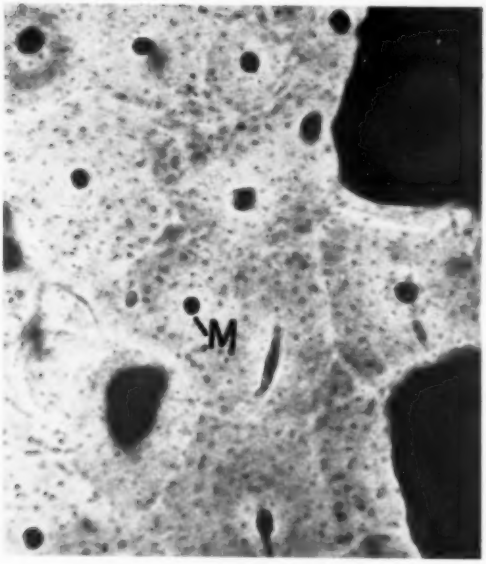

Fig. 10. Photomicrograph of a strongly exposed microradiogram of a bone specimen showing development artefacts, Mackie lines (M).

In a lightly blackened area there might appear a white line (*Mackie* line) on the border to a strongly exposed part. At our experiments this line has only been observed in some cases, for example in microradiograms of bone tissue with enormous differences in density between different parts of the image (cf. fig. 10). In microradiograms of ordinary biological tissues development artefacts, such as neighbourhood effects, could not be detected.

Defects in Film Emulsions

In case of *Lippmann* film the resolving power varies much from one emulsion number to another. The thickness of the *Lippmann* emulsion also varies. In some emulsion numbers the emulsion thickness is homogeneous enough to permit quantitative use of the films, in other ones not. Fig. 11 a illustrates the inhomogeneities in a *Lippmann* film (emulsion number 75260 2 NE), and the variations are relatively great. Fig. 11 b shows the high homogeneity of a thicker emulsion, *Eastman Kodak* 548—0. *Lippmann* film (emulsion number 24926) had the same appearance as fig. 11 b. Before starting quantitative microradiography the emulsions used must be tested for homogeneity.

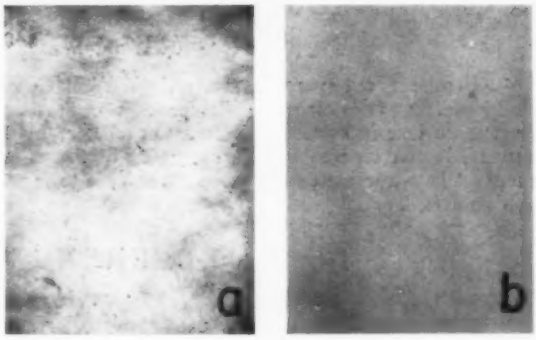

Fig. 11. Evenly exposed fine-grained plates showing the inhomogeneities in thickness and concentration of emulsion.

a. is a Lippmann emulsion 75.260—2 NE.

b. Eastman Kodak Spectroscopic Plate 548—0.

Conclusions

The fine-grained plates, commercially available at present and suitable for microradiography, permit the recording of images with a resolution as low as 1 μ in objects with strong contrast. The great variations in resolving power and homogeneity of the emulsion even within the same plate make it necessary to check the plates as carefully as possible when performing quantitative microradiographic work. The ideal plate for microradiography should have a grain size giving a resolution of about 0.5 μ and a very thin emulsion in order to keep blurring due to the geometrical arrangements in the microradiographic experiments as small as possible. The thickness of the thin emulsion must be constant in order to be able to do quantitative work. However, there seem to be certain difficulties in the manufacturing of extremely thin and at the same time even emulsion layers.

SUMMARY

The properties of fine-grained film emulsions, Lippmann emulsion, Eastman Kodak Spectroscopic Plates 548—0 and 649 have been examined with reference to their use in microradiography. Density curves, resolving power, homogeneity of emulsion, development artefacts and emulsion shrinkage have been examined for 4.50 kV roentgen rays.

ZUSAMMENFASSUNG

Die Eigenschaften von Emulsionen für Feinkorn-Filme, Lippmann Emulsion, Eastman Kodak Spektroscopie-Platten 548—0 und 649 sind in Hinsicht auf ihre Verwendbarkeit für die Mikroradiographie geprüft worden. Für Röntgenstrahlen von 4.50 kV wurden Schwärzungskurven, Auflösungsvermögen, Homogenität der Emulsion, Entwicklungsfehler und Schrumpfung der Emulsion erforscht.

RÉSUMÉ

Les auteurs ont examiné les propriétés d'émulsions de film à grain fin, à savoir celles de Lippmann et des plaques spectroscopiques 548—0 et 649 d'Eastman Kodak, au point de vue de leur utilisation en microradiographie. L'examen a porté sur les courbes de densité, le pouvoir résolutif, l'homogénéité de l'émulsion, les artéfacts dus au développement et la rétraction de la couche sensible, le tout pour une tension de Rayons Roentgen de 4.50 kV.

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FROM THE ROENTGEN DEPARTMENTS (DIRECTOR: RAGNAR STEINERT) OF THE HOSPITALS, PORSGRUNN, NORWAY

THE PROTECTIVE POWER OF ROENTGEN GLOVES[1]

by

Ragnar Steinert

It would seem that roentgenologists are to a great extent dispensing with or are seldom using roentgen gloves for their fluoroscopic work.

Braasch & Nickson (Radiology 1948) have established that of 323 roentgenologists 48 per cent showed pathological alterations in the epidermal ridges of the fingers, whilst in the non-irradiated control group, only 1.8 per cent was found. The frequency of pathological findings increased with the number of years spent in roentgen work and was upwards of 50 per cent amongst those who had been practizing for more than 15 years and 100 per cent after 35 years. »Questioning as to the use of gloves revealed that few radiologists are without leaded gloves but that their use as a routine practice is exceptionally rare.»

At the International Congress of Industrial Medicine in London 1948 it was asserted that the diurnal maximal roentgen dose on the hands should not exceed 200 milliroentgen. We cannot scientifically explain the motives of so exact a dose, but as long as we do not know whether a diurnal roentgen fluoroscopy of the hands of this order of magnitude is entirely safe, one should aim at reducing this irradiation as much as possible and preferably eliminate it entirely. By using serviceable roentgen gloves this can easily be done.

I am going briefly to give an account of some experiments, where the aim has been to ascertain:

1. How large a roentgen dose per time-unit do the bare hands receive during the usual fluoroscopic work?
2. How large a roentgen dose per time-unit do the hands receive when protected by roentgen gloves of varying lead equivalent?

The leaded rubber which is being used in gloves has as a rule a lead equivalent of 0.1—0.7. That is to say that a plate of leaded rubber of a

[1] Read at the 6th International Congress of Radiology in London 1950; submitted for publication, Sept. 18, 1950.

thickness of one millimeter protects in the same degree against roentgen rays as a leaded plate of 0.1—0.7 mm.

The roentgen doses in these experiments were measured by condensor chambers possessing a sensitivity of 5 mr and a maximum capacity of 300 mr. The measurements are being carried out by Mr. K. FINBORUD, Physicist of the State's Physical Laboratory, Norway, whose director is Dr. N. H. MOXNES.

The condensor chambers were pushed as far into the gloves as possible and were fully covered by the glove. On account of their relatively large diameter, the end of the condensor chambers did not quite reach the fingertips. For this reason one must suppose that the doses received by the fingers are somewhat greater than the dose measured on the palm of the hand. The experiments were carried out partly with the usual operation gloves in order to determine the doses which the unprotected hands are receiving, partly with roentgen gloves of American, French, and Norwegian makes, with lead equivalents of 0.5—0.28 and of 0.2.

The experiments were carried out partly on standing and partly on recumbent patients. In the latter case the glove which was to be tried was usually placed on the abdomen with an inlaid wax phantom of the same thickness and shape as the hand. The condensor chambers were then placed between the volar side and the phantom and nearer the tube than the latter. For the experiments with standing patients two types of stands were used — 1) the Siemens stand of the latest type with an explorator and with good protection of all handles, and 2) the Kock & Sterzel stand of a somewhat older type with a presumably somewhat less efficient protection. The control of the roentgen tube is — on both stands — performed by the left hand while the shade of the Siemens stand is directed by the left hand and of the Kock & Sterzel stand by the right hand. Only the actual screening time was recorded with a stop watch.

As might be expected, the doses measured varied — per time-unit — in the various experiments. In most experiments the hands will actually be irradiated for only a small part of the aggregate fluoroscopic time. This is clearly brought out in some experiments where the patients were partly screened standing, while their stomach was examined, partly while they were having their colon screened, lying flat on their back. In the latter case, the gloves were placed on the abdomen of the patient and were removed together with the tube in such a manner that the condensor chambers were, practically speaking, struck by the central ray during the whole experiment. In the meantime a dose of fluoroscopy of from 18 mr up to 27 mr per minute was measured, whilst in the former case — with the patient erect in the frame and with the hand of the investigator in continual movement — only 2.4 mr per

minute was measured. These experiments do not allow any direct comparison, because, amongst other reasons, the same patients were not examined standing and lying down. They show, however, that the total fluoroscopic time does not necessarily constitute any measure of the risk to which the roentgenologist is exposing his hands.

The experiments with bare hands — and using the Siemens stand — showed — in the case of the right hand — an average dose of about 8 mr per minute, and — in the case of the left hand — of about 4 mr per minute. As to the Kock & Sterzel stand, the corresponding figures were about 6.8 mr, and about 4.6 mr. All the experiments showed that the right hand received a larger roentgen dose, and, as a rule, double of that received by the left hand. All of the experiments were carried out with a constant fluoroscopy of 70 kV and 3—4 milliampère.

The experiments in fluoroscopy with unprotected hands thus tend to show that the doses one is being exposed to are quite considerable. If we are safe in setting out with the assumption that our results are of universal value, we must suppose that every one who is working with the Siemens stand will — in the course of a fluoroscopy of about half an hour — have received the allowed tolerance dose on his right hand.

As already mentioned, the examined roentgen gloves had a lead equivalent of respectively 0.2—0.28, and 0.5.

After the use of gloves with an equivalent of 0.2, the condensor chambers show varying readings from 66 mr to 130 mr, according to the fluoroscopic time from 3 minutes to well over 26 minutes. When using gloves with an equivalent of 0.28, the readings are considerably less, from a little over 40 minutes of fluoroscopy, only 13.5 mr. When using gloves with an equivalent of 0.5, the readings range between 5—20 mr, after screening from 5 to 44 minutes. Doses of less than 10 mr could not be measured very accurately, because the condensor chambers do not easily lend themselves to such small doses. It is therefore probable that some of the doses, which have been measured during the use of gloves of an equivalence of 0.5, may actually be too high.

As already mentioned, the results varied considerably, in the individual experiments, and in order to obtain more reliable figures, it is necessary to undertake a greater number of experiments. This will be done.

The experiments with roentgen gloves thus show that gloves with a lead equivalent from 0.1 up to 0.2 are entirely unsatisfactory in roentgen departments where the fluoroscopic time may reach one hour or more per day for the individual investigator. With an equivalent of 0.28, the doses are considerably smaller. With this thickness of the lead it ought to be possible to work for several hours without exceeding the tolerance limit. With an equivalent of 0.5, one may, practically speak-

ing, say that the hand is perfectly protected. Therefore it should not be necessary to use roentgen gloves with a higher equivalent.

The lead equivalent stated by the factory was controlled in every individual case. In two instances, the results did not tally. In the one instance, the factory stated: »usually a lead equivalent of 0.3—0.4». But our result showed 0.2. In another instance, the factory stated 0.35, while the control showed 0.28. The cause of these differences may, amongst other things, be that the factories are fixing the lead equivalent with such a low kilovolt that the rubber will act as a protection. At our control the equivalent was fixed at 80 kV.

SUMMARY

The protective power of roentgen gloves has been measured by condensor chambers which were placed inside the glove. Gloves with a lead equivalent of 0.2—0.5 have been used. In the same way it was investigated how large a roentgen dose the unprotected hands received. With the screening technics used by the author the diurnal maximal roentgen dose on the hands was exceeded in a relative short time.

ZUSAMMENFASSUNG

Der Strahlenschutz von Röntgenhandschuhen wurde mit Kondensator-Kammer gemessen die in den Handschuh gesteckt wurden. Verwendet wurden Schutzhandschuhe mit einem Blei-Äquivalent von 0.2—0.5. In der gleichen Weise wurde untersucht, wie hoch die Röntgendosis ist, die die ungeschützten Hände erhalten. Bei der Durchleuchtungstechnik, mit der von dem Verfasser gearbeitet wird, wird die tägliche Maximaldosis an den Händen in einer verhältnismässig kurzen Zeit erreicht.

RÉSUMÉ

L'auteur a mesuré le degré de protection procuré par des gants à Rayons Roentgen en plaçant des chambres condensateurs à leur intérieur. Il s'est servi de gants à équivalent plombique de 0.2 à 0.5. Il a recherché de façon semblable quelle dose de rayons recevait la main nue. Avec les écrans qu'il emploie la dose journalière maxima permise pour les mains a été dépassée en un temps relativement court.

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FROM THE RADIOTHERAPY DEPARTMENT (DIRECTOR: PROF. D. W. SMITHERS)
OF THE ROYAL CANCER HOSPITAL, LONDON, ENGLAND.

SOME VARIED APPLICATIONS OF RADIOACTIVE ISOTOPES TO THE LOCALISATION AND TREATMENT OF TUMOURS[1]

by

D. W. Smithers

The subject of this symposium, the use of radioactive isotopes in therapy, has attracted wide interest throughout the medical profession and indeed amongst the lay public as well. Many doctors who previously showed little interest in radiotherapy have not only taken notice, but in some cases have also started treatment. The situation is full of promise, opportunity and danger. Promise as this may perhaps be one of the really significant advances in medical practice of our day; opportunity since the influx to radiotherapy of new people with wide experience and new ideas must in the end help us forward; and danger because it has attracted some people who, while they would hesitate to treat a patient with a 2 MeV roentgen therapy plant, feel quite prepared to inject a radioactive isotope solution emitting 2 MeV roentgen rays.

It is only sixteen years ago that FERMI and his collaborators (1934), the JOLIOTS (1934) and E. O. LAWRENCE (1934) all announced the artificial production of radioactive isotopes in the same year, and fourteen years ago on the 23rd March, that HAMILTON and STONE (1936) treated the first patient with cancer with radioactive sodium. So little time! Time for the first wave of enthusiasm to have subsided, the sensible words of caution of the pioneers to have been appreciated and, as we have heard to-day, for preliminary assessments to be made; time for mistakes in plenty, but hardly time for wisdom. If this is so for our American colleagues, what of us? At the Royal Cancer Hospital we treated our first patient with an artificial radioactive isotope a little less than two years ago and have only recently treated our one hundredth. We are naturally

[1] Paper read at the Sixth International Congress of Radiology, London, 1950; submitted for publication, Sept. 20, 1950.

THE TREATMENT OF 96 PATIENTS WITH CANCER BY MEANS OF RADIOACTIVE ISOTOPES AT THE ROYAL CANCER HOSPITAL IN 18 MONTHS FROM DECEMBER 1948 TO JUNE 1950.

DIAGNOSIS	NUMBER OF PATIENTS.	ISOTOPE	METHOD OF ADMINISTRATION.
LYMPHOSARCOMA · RETICULOSIS LEUKAEMIA.	21	P^{32}	INTRAVENOUS INJECTION
MISCELLANEOUS MALIGNANT TUMOURS	20	P^{32}	INTRAVENOUS INJECTION
POLYCYTHAEMIA VERA	17	P^{32}	INTRAVENOUS INJECTION
CARCINOMA OF THE THYROID.	14	I^{131}	BY MOUTH.
CARCINOMA OF THE BLADDER.	14	Na^{24} Br^{82}	INTRA-VESICAL BAG
CARCINOMATOSIS PERITONEII	5	A_U^{198}	INTRAPERITONEAL INJECTION
MISCELLANEOUS MALIGNANT TUMOURS.	3	T_A^{182}	INTERSTITIAL WIRING
CARCINOMA OF THE BREAST.	1	A_U^{198}	TUMOUR INFILTRATION
BASAL-CELL CARCINOMA.	1	P^{32}	IN POLYTHENE AS SURFACE APPLICATOR.

Fig. 1.

conscious of the fact that we are building on a foundation of many years experience of the application of ionising radiations to patients but feel the necessity of reminding ourselves, as well as of making it clear to you, that in this field we are still beginners with a great deal to learn.

Before making general observations on the use of radioactive isotopes in malignant disease it therefore seems to me to be desirable that we should state precisely what we have done. An account of our work has already been given by WALTON (1950) and some repetition is necessary here if the picture is to be complete. In the first 18 months we treated 96 patients with cancer and used radioactive isotopes in just over 50 others during the same period as a method of investigation for the purpose of tumour localisation, assessing the directions and degree of spread of the disease and to see if the relative absorption in tumour tissue rendered them suitable for treatment. Fig. 1 sets out these 96 cases.

At the same time iodine was used as an aid in diagnosis for patients with retro-sternal swelling; phosphorus to see how it was taken up in

tumours of the skin and breast, and diiodo- and dibromo-fluorescene for attempted tumour localisation in patients suspected of having cerebral tumours. This work on the localisation of brain tumours is being reported to this congress later in the week by Dr. J. G. DE WINTER and Mr. E. H. BELCHER. I had hoped to report to you the first measurements made on patients with carcinoma of the breast using Professor W. V. MAYNEORD's subcutaneous needle scintillation counter for probing the axilla and parasternal spaces but, although the apparatus is completed and working in the laboratory, preparations for an international congress have somewhat delayed our clinical progress.

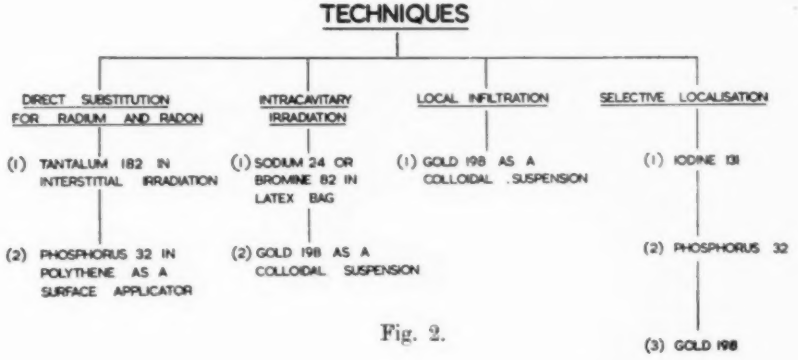

TECHNIQUES
DIRECT SUBSTITUTION FOR RADIUM AND RADON
(1) TANTALUM 182 IN INTERSTITIAL IRRADIATION
(2) PHOSPHORUS 32 IN POLYTHENE AS A SURFACE APPLICATOR
INTRACAVITARY IRRADIATION
(1) SODIUM 24 OR BROMINE 82 IN LATEX BAG
(2) GOLD 198 AS A COLLOIDAL SUSPENSION
LOCAL INFILTRATION
(1) GOLD 198 AS A COLLOIDAL SUSPENSION
SELECTIVE LOCALISATION
(1) IODINE 131
(2) PHOSPHORUS 32
(3) GOLD 198

Fig. 2.

This activity has entailed a great deal of work in the physics department, the development of a whole new organisation within the hospital and the evolution of a number of new treatment techniques (Fig. 2). We are feeling our way, learning our lessons and trying to balance our natural inclinations to try new ideas at once, against our responsibility both to our patients and our staff which demands that we proceed with the greatest care and circumspection.

Our first step was to try and reproduce what seemed to be the most successful treatment that had so far been evolved, namely the use of P 32 for patients with polycythaemia vera. Combined with venesection this has appeared to us to be a satisfactory form of treatment for the disease, our initial responses following closely those reported by J. H. LAWRENCE (1948).

At the same time P 32 was given to a number of patients with leukaemia and various forms of reticulosis and to others with disseminated carcinomatous metastases in varying doses and at various intervals. This group cannot be assessed as yet but valuable experience is accumulating. To give two examples. One a policeman of 55 with chronic

lymphatic leukaemia who came to us in March 1949 thin, pale and weak, with ascites, pleural effusion, a large spleen and generalised lymphadenopathy. He received 6 injections of P 32 of approximately one millicurie each at weekly intervals and absorbed his effusions, lost his palpable swellings and has felt fit and well for the past year. Even if this remission is no better or longer than might have been produced with roentgen therapy, which in this case seems unlikely, it was at least obtained with no discomfort whatever and with a considerable gain in convenience to

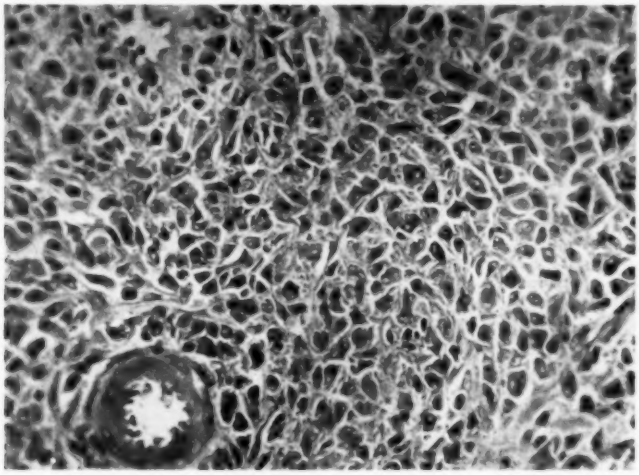
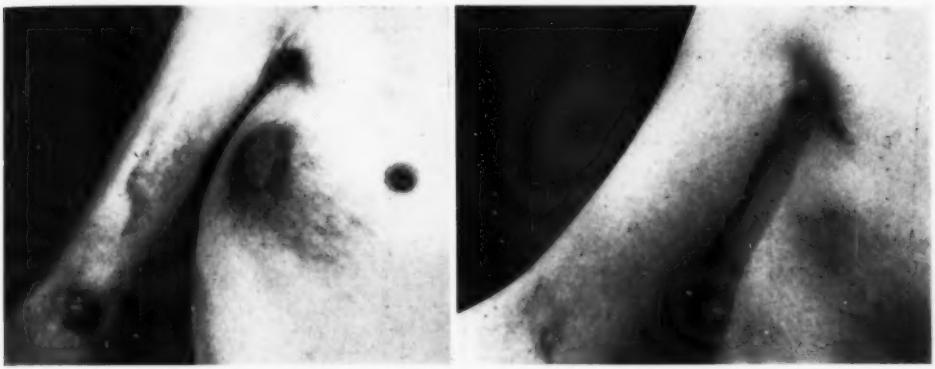


Fig. 3. Photomicrograph of a portion of tumour removed from the stomach of a woman of 24 years of age treated with P 32.

both the patient and the radiotherapy department. The other a schoolteacher of 24 had had a partial gastrectomy in April 1948 for a tumour of the stomach (Fig. 3), and came to us in May 1949 weighing 6 st. 1 lb. (= about 39 kg) with gross wasting and dehydration, obstruction of the lower end of the oesophagus and multiple secondary deposits in the skin, breast, thyroid and lymph nodes on both sides of the neck and with a palpable mass in the epigastrium. Clinically this appeared to be a lymphosarcoma of the stomach, but the pathologists with plenty of material from two sites to examine have maintained throughout that it was an anaplastic carcinoma. She was given roentgen therapy to the obstruction at the cardia for immediate and urgent relief of symptoms, had a lymph node removed from the neck to compare with the tumour previously removed from the stomach and had a test dose of 1 millicurie of P 32. Counting rates over the skin tumours were



(a) 21. 7. 49 before treatment. (b) 4. 11. 49 after treatment.

Fig. 4. Two of the multiple secondary deposits in the skin in the same patient shown in Fig. 3.

at least 5 : 1 over the normal skin, so she was given a therapeutic dose of 5 millicuries of radioactive phosphorus. There was rapid and complete regression of all visible and palpable masses (Fig. 4), the patient swallowed well, gained more than 6 kg in weight, and pieces of skin and subcutaneous tissue removed from the centre of the position previously occupied by a large secondary deposit showed slight dermal thickening only. 4 months later she developed a recurrence of the swelling in the right lobe of the thyroid, this was treated locally with roentgen-rays and disappeared, but a month after that she had an epileptic fit, became depressed, lost her appetite and began to lose weight. It was thought that she had developed secondary deposits in the brain and two further injections of 5 millicuries of P 32 were given, one in December 1949 and one in February 1950, without improvement. She steadily deteriorated, developing headache and slurring of speech, became disorientated

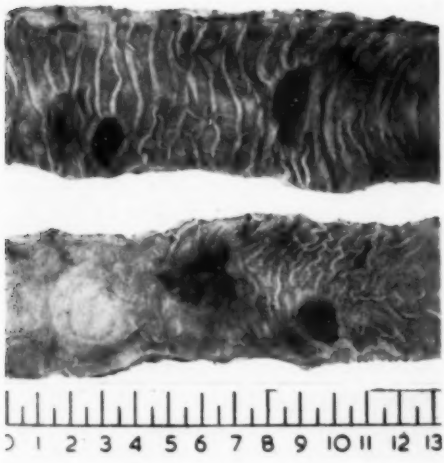


Fig. 5. Some of the ulcers of the bowel found at autopsy in the patient shown in Figs. 3 and 4.

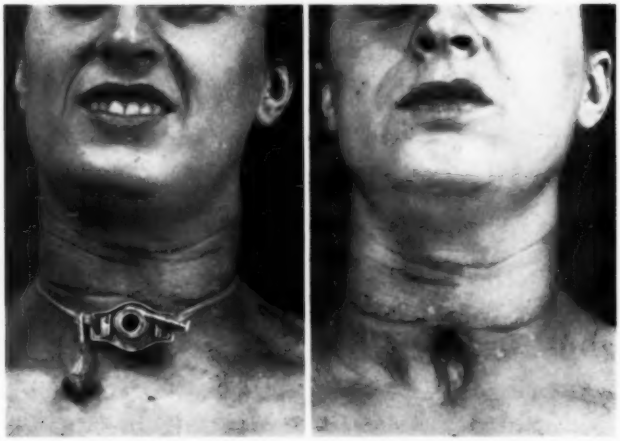


Fig. 6 a. Fig. 6 b.

Fig. 6 a. Woman aged 20 with carcinoma of the thyroid and secondaries in neck nodes and in lungs before treatment with I 131.
Fig. 6 b. Same patient six months after the first treatment with radioactive iodine.

and died last March. At post mortem examination no sign of residual tumour could be found at any site, there was an area of necrosis in the left cerebrum and a number of intestinal ulcers all free from growth (Fig. 5). Dr. J. W. WHITTICK the pathologist who performed the post mortem examination summed up by saying:

»It would appear that all metastases from the original growth in the stomach have been destroyed by radiotherapy. The brain and intestinal lesions possibly represent sites of metastasis which now show only reactive and reparative changes. If this is so, lymphosarcoma can almost certainly be excluded from the diagnosis. Anaplastic carcinoma, on the other hand, would be likely to produce cerebral metastases. The histology of the biopsy material received earlier supports the diagnosis of anaplastic carcinoma.«

May I suggest that whether adenocarcinoma or lymphosarcoma this patient died from necrotic ulcers of the brain and bowel following the »cure« of widespread disseminated cancer; that the last two injections given would have been better withheld; that even the destruction of every cancer cell may not always be enough; and that we must now remember to be on the look out for necrosis and failure to heal in unsuspected regions at a depth in the body as a new factor in radiotherapy.

Our experience with I 131 in thyroid carcinoma is slender but we have a few patients of some interest and one who is quite fascinating. This patient (Fig. 6) a girl just 20 years of age arrived in April 1949 with a history of 10 months swelling of the neck and hoarseness of the

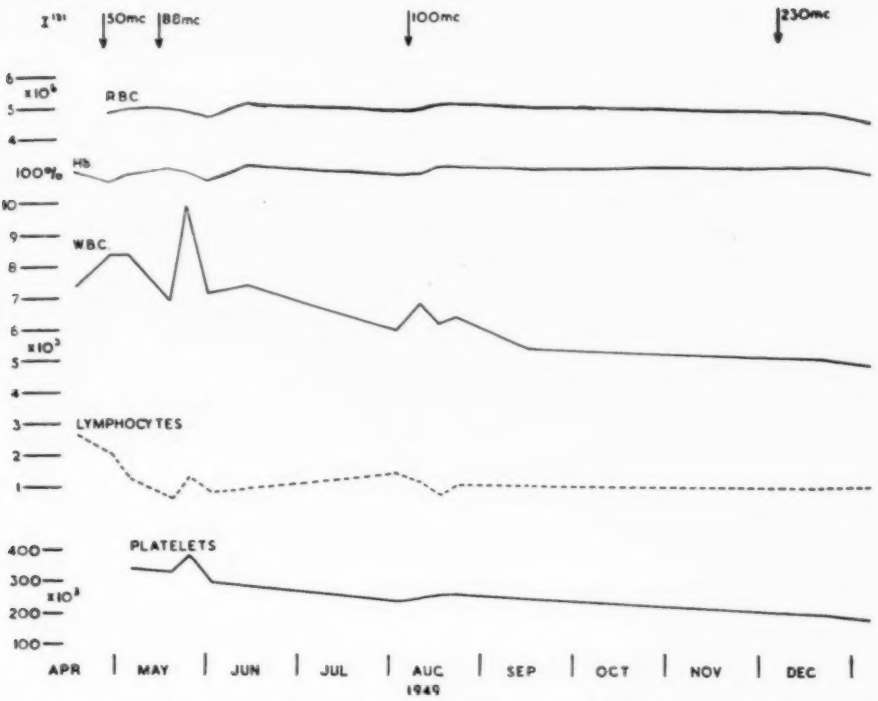


Fig. 7. Chart showing treatment given and response of blood cell counts in patient shown in Fig. 6.

voice. Two months before an attempt had been made to remove her thyroid tumour but it was so adherent that only the isthmus could be excised. A tracheotomy had been performed. She had a hard fixed thyroid tumour, enlarged hard nodes on both sides of the neck, complete tracheal obstruction and multiple secondary deposits scattered throughout both lungs. She was both ill and alarmed. A lymph node was removed, the diagnosis of well differentiated, colloid forming adenocarcinoma confirmed, and a test dose of 70 microcuries of I 131 given with such a good uptake in primary and nodes that therapeutic doses were then prescribed (Fig. 7). She had in all doses of 50, 88, 100 and 230 millicuries over a period of 7 months. Radiographs were taken and they showed the outline of the neck and bases of both lungs by laying the patient on a roentgen film. The radiation from both neck and lungs could also be detected quite easily with a fluorescent screen. She has responded very well, no tumour is detectable now (Fig. 6 b), her tracheotomy has been closed, the chest

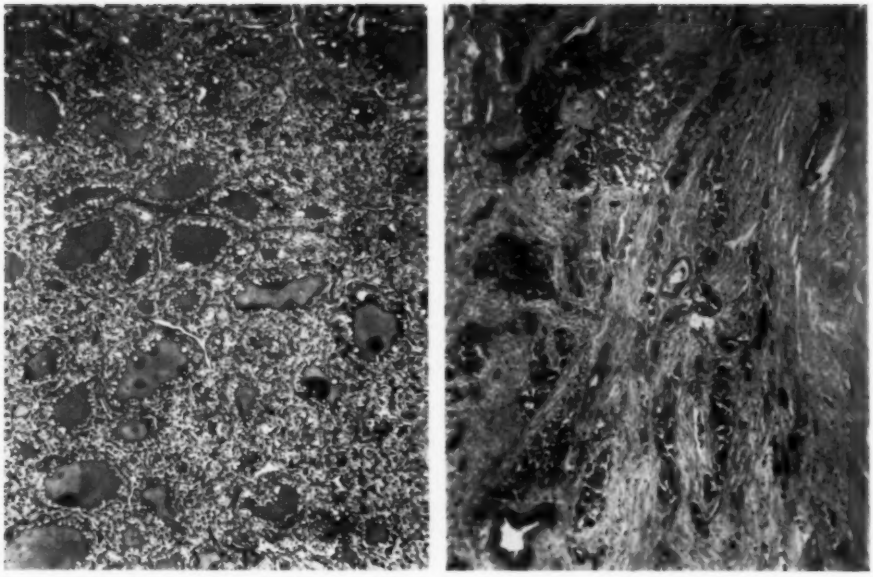


Fig. 8 a. Fig. 8 b.

Fig. 8. Change in histological appearance during treatment — patient shown in Figs. 6 and 7.

roentgenogram is practically normal, she has gained weight but has not so far required any thyroid extract. The change in histological appearance during treatment is shown in Fig. 8. She is well and symptom-free 15 months after she first arrived at the hospital.

The technique of bladder irradiation has already been described by WALLACE, WALTON and SINCLAIR (1949); I merely propose to show you some illustrations of the technique (Figs. 9, 10 and 11) and to say that we persist in our original impression that this is a useful new method of treatment for multiple superficial bladder tumours. A similar method has been used by MULLER (1949) who boldly filled a bag in the bladder with a solution of cobalt 60.

Intra-peritoneal injections of colloidal gold, were given to five patients, once shortly before death so as to observe its distribution and four times as treatment for carcinomatosis peritonei. One of these patients, a woman of 41 was treated by Mr. LEDLIE with a radical mastectomy for carcinoma of the breast in January 1947, she remained well until January of this year when she had a rapid onset of abdominal swelling and was found to have ascites and an ovarian tumour. At operation Mr.

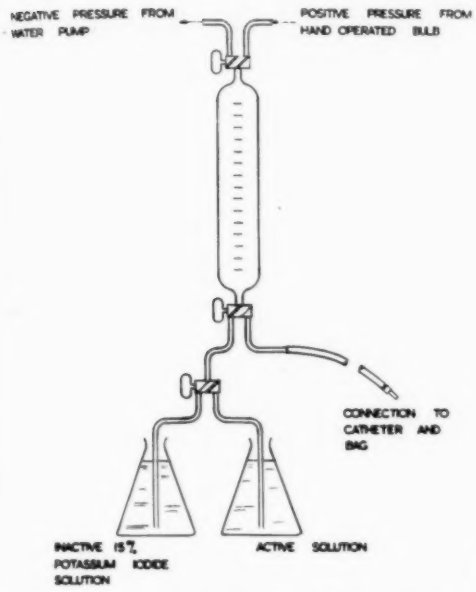

NEGATIVE PRESSURE FROM WATER PUMP
POSITIVE PRESSURE FROM HAND OPERATED BULB
CONNECTION TO CATHETER AND BAG
INACTIVE 15% POTASSIUM IODIDE SOLUTION
ACTIVE SOLUTION

Fig. 9. Apparatus for filling intravesical bag with inactive and active solutions.

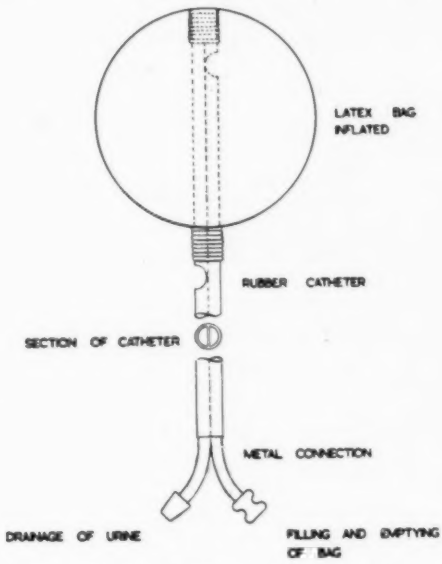


Fig. 10. Latex bag for intracavitary irradiation of the bladder.

Douglas MacLeod found bilateral papillary carcinoma of the ovaries, ascites and the whole peritoneal surface studded with secondaries. Both ovaries were removed and an intraperitoneal injection of 95.5 millicuries of colloidal gold 198 in 1,000 cc of saline given shortly afterwards. She had some flatulence and discomfort after food for a few weeks but has otherwise remained well for six months since her treatment, had no return of ascites and has recently opened up a new business. She and the three others since treated are being followed with interest. Dr. Muller of Zurich has been using a similar technique and is reading a paper on this subject to the congress this week. We have measured the γ-ray dose received by an ionisation chamber swallowed before treatment and passing through the intestine during the period of activity of the gold. This has proved to be an interesting observation, the physics department having predicted the γ-ray dose that would be measured with remarkable accuracy.

Our other experimental treatments have been tantalum wire implants by my colleague Dr. M. Lederman (Fig. 12), tumour infiltration with colloidal materials to note the local effect and to follow the path of the

Fig. 11. Radiograph of the latex bag when inflated in the bladder for treatment.

Fig. 12. a. Orbital tantalum wire implant.

Fig. 12 b. Tantalum wire implant of the palate.

particles and the use of phosphorus impregnated plastics as surface applicators (Fig. 13), an extension of a method using thin blotting paper put forward by LOW-BEER (1946). These are only in the first stages of development though the numbers shown in Fig. 1 for the first eighteen months of our work are now a little larger.

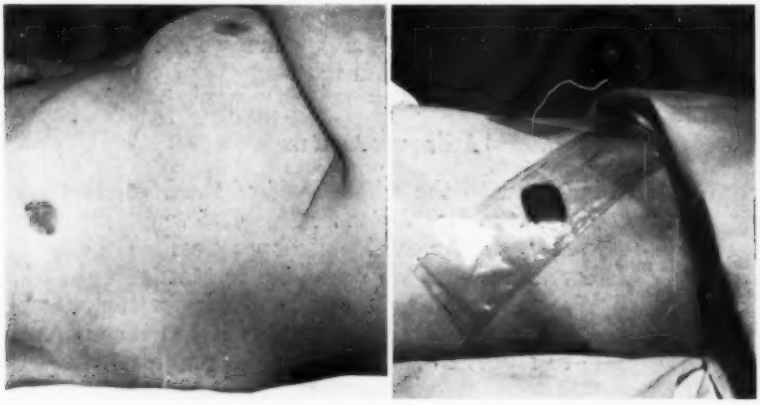


Fig. 13 a. *Tumour.*

Fig. 13 b. Plaque in place, sealed in thin transparent sheet to prevent contamination.

Figs. 13 a and b. One tumour in a patient with multiple superficial basal-cell carcinomata being treated with plastic sheet impregnated with radioactive phosphorus.

Conclusions

In the papers that we read to each other we usually end by presenting a survival rate which we have hopefully worked on until it is a little bit better than somebody elses. I have had nothing to offer you but an account of individual patients treated by developing techniques, but if we are still unable to present a balanced view we can at least affirm that the field of radiotherapy has been expanded and its effectiveness in the investigation and treatment of cancer improved. The employment of radioactive isotopes as a means of investigation of the development, localisation, spread and control of cancer appears to offer great opportunities. Their use for interstitial, surface or beam therapy offers an extension of treatment along established lines. The value of radioactive isotopes for general clinical use by mouth or injection is not yet so certainly established but the introduction of this method of treatment has enabled us to produce effects which were not previously obtainable; some, such as the occasional regression of multiple disseminated tumours, even if they come too late or are not permanent at least offer great temporary benefit and hope of progress. If radioactive isotopes are handled with skill and care we should improve our radiotherapy techniques but if they are to be rapidly adopted by untrained enthusiasts they

are more likely to produce our next crop of medical martyrs. To the radiotherapist they offer new opportunity which we are glad to welcome and which we hope to learn to use aright.

Acknowledgment

I am greatly indebted to the whole staff of the Radiotherapy and Physics Departments of the Royal Cancer Hospital whose close association makes our work with radioactive isotopes possible. It is due to Professor W. V. MAYNEORD that we were able to start this work at all, and to Dr. R. J. WALTON who has been responsible for the clinical and Mr. W. K. SINCLAIR for the physical side that it has been carried out, and that I am able to report to this congress the progress that we have so far made together.

SUMMARY

The first eighteen months' work with radioactive isotopes in the localisation and treatment of malignant tumours at the Royal Cancer Hospital in London is reported. Examples of the use of Iodine 131, phosphorus 32, and gold 198 for selective localisation, of gold 198 as a colloidal suspension for local infiltration and intra-cavitary injection, of sodium 24 and bromine 82 for intra-cavitary treatment in a latex bag, of tantalum 182 for interstitial implantation, and of phosphorus 32 in polythene as a surface applicator, are given.

ZUSAMMENFASSUNG

Es wird Bericht gegeben über die Arbeit der ersten 18 Monate mit radioaktiven Isotopen zur Lokalisation und Behandlung bösartiger Geschwülste am Royal Cancer Hospital in London. Es werden Beispiele gebracht für die Anwendung von Jod^{131}, Phosphor^{32} und Gold^{198} zur selektiven Lokalisierung, von Gold^{198} als kolloidale Suspension zur örtlichen Gewebsinfiltrierung und zur intracavitären Injektion, von Natrium^{24} und Brom^{82} zur intracavitären Behandlung in einer Latex-Blase, von Tantal^{182} zur interstitiellen Implantation und von Phosphor^{32} in »Polythene« als Oberflächen-Applikator.

RÉSUMÉ

Compte-rendu des dix-huit premiers mois de travail avec les isotopes radioactifs, au Royal Cancer Hospital de Londres, pour localiser et traiter les tumeurs malignes. Exemples de l'emploi de l'iode 131, du phosphore 32 et de l'or 198 pour la localisation sélective; de l'or 198 à titre de suspension colloïdale pour les infiltrations locales et les injections intracavitaires; du sodium 24 et du brôme 82 pour les traitements intracavitaires dans un sac de latex; du tantale 182 pour l'implantation interstitielle; enfin du phosphore 32 en application de surface dans des polythènes.

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FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT (DIRECTOR: PROF. OLLE OLSSON) OF THE UNIVERSITY CLINICS OF LUND, SWEDEN

MAGNETIC GUIDANCE OF A CATHETER WITH ARTICULATED STEEL TIP[1]

by

Hans Tillander

The last few decades have witnessed rapid methodological advances and technical improvement in angiography, a method now finding a wide range of applicability. Two different techniques have been devised: venous or arterial puncture followed by injection of contrast medium; or introduction of a catheter and deposition of the contrast medium in or as near as possible to the region to be examined. The former technique has been employed in the visualization of the carotid artery (MONIZ, 1927), of the aorta and its branches (DOS SANTOS, 1937) and for roentgenography of the heart and pulmonary vessels (ROBB, STEINBERG, 1939).

The latter technique is of later date, but during recent years it has found increasing application, especially since the advent of cardiology. In the beginning a catheter was introduced into the venous system and contrast medium deposited in the vena cava or in the right half of the heart, and the passage of the contrast medium through the heart and the lungs followed by serial roentgenography (FORSSMAN, 1929, 1931; and others). In 1941 FARIÑAS described catheterization of the arterial system via the femoral artery and claimed good results. In 1947 RADNER published a method of catheterization of the vertebral artery by means of a guidable catheter, introduced via the radial artery. He also employed this method for the visualization of the thoracic aorta, coronary arteries and for the cranial branches of the subclavian artery (1949).

Catheterization offers several advantages. Deposition of highly concentrated solutions of contrast medium into the perivascular tissue is avoided, besides which solutions of lower concentration may be employed, because the closer the contrast medium is deposited to the site to be examined the less it will be diluted by the circulating blood. The use

[1] Submitted for publication, Sept. 21, 1950.

of contrast medium of relatively low concentration is by no means an advantage of minor importance. It has been demonstrated that injection of highly concentrated solutions of radiopaque medium is sometimes followed by injuries, particularly to the central nervous system (BROMAN & OLLE OLSSON, 1949).

Catheterization called for a method whereby the catheter may be directed from without. RADNER (1949) met this requirement by providing the lumen of the catheter with a curved elastic steel wire. With some practice and a good knowledge of the topography of the vessel complexes to be examined, the method will usually answer the purpose. In an endeavour to devise a method that would *always* be practicable I have for some years tried to guide the tip of the catheter by means of a strong magnetic field set up near the site to be examined. The tip of the catheter consists of small steel-links connected to one another by ball and socket joints permitting a maximum universal angular movement of about 20 degrees between any two consecutive links. In order to prevent rust formation, the links are gold plated. The lines of force emitted from a magnetic pole describe a multitudinous variety of curves, which may be utilized to direct the tip of the catheter along any imaginable curve or bend and in any desired direction. As the tip of the catheter will be given a permanent magnetism when used for the first time, it will afterwards be either repelled or attracted by the magnetic pole according to the polarity of the latter at subsequent examinations.

In preliminary experiments on corpses and on living dogs use was made of a magnet of solenoid type with a massive iron anchor about 5 cms in diameter. It was energized by 220 volts with an intensity of 5 ampères and thus consumed 1,100 watts. This magnet was found strong enough for use on dogs and on lean corpses. In the present study interest was focused mainly on the branches of the abdominal aorta, and it was observed that under favourable conditions the catheter could be guided into any one of the arterial branches with a calibre large enough to permit the passage of the catheter. The catheter was introduced through the left radial artery and the descending aorta. The application of the method is, of course, not limited to the arterial system, but may be employed for the venous system and the bronchial tree, for example.

Technical experiments carried out by Aktiebolaget ASEA have shown that if the magnet is to be strong enough to satisfy clinical requirements, it must have a power output of about 5.4 kw. and a diameter of about 50 cms and would then weigh about 200 kgs. The construction would present no technical difficulties. The magnet need be movable only in the horizontal plane, over or underneath the patient. Attempts to improve upon the method are in progress.

SUMMARY

A preliminary report is given of a method for directing a catheter into desired vessel or duct by providing the catheter with an articulated steel-tip and directing the passage of the latter by means of a strong magnetic field.

ZUSAMMENFASSUNG

Vorläufige Mitteilung einer Methode, bei der ein Katheter in die gewünschte Gefässabzweigung oder andere kanalartige Hohlräume geleitet wird. Der Katheter ist mit einer gelenkigen Stahlspitze versehen und wird dem Einfluss eines starken Magnetfeldes ausgesetzt.

RÉSUMÉ

Rapport préliminaire sur une méthode permettant de diriger une sonde dans une branche vasculaire ou d'autres cavités canaliculaires, en la munissant d'une pointe d'acier dirigeable qu'on soumet à un puissant champ magnétique.

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FROM THE ROENTGEN DIAGNOSTIC DEPARTMENT (DIRECTOR: OLLE OLSSON)
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ANTIHISTAMINIC DRUGS FOR INHIBITING UNTOWARD REACTIONS TO INJECTIONS OF CONTRAST MEDIUM[1]

by

Olle Olsson

Untoward reactions to intravenous injections of contrast media administered in connection with urography, for example, are common. These reactions often consist of coughing, sneezing, nausea, and a few separate or widespread urticarial lesions. In addition hereto shock, sometimes even death, may occur (HULTBORN 1939, JUNGMICHEL 1940, PENDERGRASS et al. 1942, SIMON 1948, OLLE OLSSON 1949, and others).

In an endeavour to avoid these side reactions attempts have been made to predict any hypersensitivity by careful inquiry into the family and personal history for allergy, and by certain tests, etc. Judging by our experience these measures are of fairly limited value. This is confirmed by a comparative study of different tests carried out by ALYEA & HAINES, 1947.

These precautionary measures are very time-consuming. Another disadvantage is that they will not reveal all patients hypersensitive to the contrast medium and secondly, that the procedure will exclude certain patients well able to tolerate the contrast medium, and thereby deprive them of the possibility of a valuable examination.

A more rational approach would be to try to inhibit the untoward reactions. This would perhaps be possible by using a contrast medium of a type other than those hitherto used. Until new satisfactory contrast media are available, the writer has decided to try the prophylactic approach *using antihistaminic drugs*.

Antihistaminic Drugs. General Considerations

It is known from animal experiments that local and general liberation of histamine is an accompaniment of allergic reactions. Histamine has

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therefore been given much attention in the discussion of the causation of anaphylactic reactions. It was BOVET & STAUB's (1937) paper on the possibility of inhibiting the shock effect of histamine that first aroused the great attention that has been given to antihistaminic drugs. This name includes a large number of substances capable of inhibiting histamine and thereby also capable of warding off or damping anaphylactic reactions. Several antihistaminic drugs differing as regards chemical composition and pharmacological properties and sold under different trade marks are now available. According to MEYER & BUCHER (1948), these substances exert the strongest inhibitory action upon the histaminic effects on the smooth muscle, slightly less on vascular effects, and hardly any on those effecting glandular secretion. They also stress that these substances ought not to be expected to control all allergic reactions, for it is still unknown whether all antigen-antibody reactions are accompanied by a liberation of histamine.

Antihistaminic drugs have been employed in the treatment of many kinds of hypersensitive reactions and a voluminous literature on their clinical use and value is available (KALLÓS and KALLÓS-DEFFNER 1949). The favourable results reported by critical workers induced the writer to try the value of antihistaminic drugs in the prophylactic treatment of untoward reactions to contrast media.

Antihistaminic Medication in Association with the Injection of Contrast Medium

a) *Examination Series*

In an endeavour to obtain as uniform a series as possible the examinations were carried out in connection with the injection of contrast medium for urographic examinations of adults. The amount of contrast medium injected was uniform throughout, as was also the injection technique (including the injection time) employed in one group in which the patients were pre-medicated with an antihistaminic substance and in a control group without such pre-medication. The figures deduced from the reactions recorded are perhaps not quite unobjectionable for statistical treatment, because the examiner administering the injection had, of course, to know what he was injecting. Personal bias was minimized by carrying out the examinations on a large series and by allowing different examiners to administer the injections and judge the reactions.

One rule strictly adhered to was not to allow the contrast medium to remain any length of time drawn up in the syringe.

The reactions described below were observed immediately after, or within a short time of, the injection. Any reactions appearing some hours after the injection were therefore not taken into account.

In the first trials use was made of the antihistaminic substance. Antasten (Ciba) of which 2 ml were injected subcutaneously or intramuscularly 30 to 60 minutes before the intravenous administration of the contrast medium. The encouraging results discovered in this preliminary investigation were reported in Swedish Association for Medical Radiology, 1949. Later CREPEA, ALLANSON & DE LAMBRE (1949) reported similar trials in New York State Journal of Medicine and conclude: »pre-medication with Pyribenzamine or Trimeton did not seem to influence the incidence, severity or type of reactions to Diodrast.» This negative result may possibly be due to the administration of an insufficient quantity of antihistaminic substance or the injection might have been given too short a time before the injection of the contrast medium.

In order to avoid the necessity of two injections and to obtain a more concentrated effect of the antihistaminic substance the above-mentioned preliminary tests were followed by trials in which the contrast medium was mixed with the antihistaminic substance before injection. In these tests use was made of Desentol »Leo» (loc. Benadryl) in a dose of 20 milligrams mixed in Dijodon »Leo» 35 per cent (loc. Diodrast). The contrast medium with incorporated antihistaminic substance is called Dijodon D. Experiments on guinea-pig gut showed that the antihistaminic substance retains its inhibitory effect on histamine in spite of the incorporation of the contrast medium.

The dose of 20 milligrams antihistaminic substance occasionally caused slight drowsiness. No other side effects were observed after the injection of Dijodon D.

No patient was exempted from the examination on account of allergy. On the other hand, after the favourable results obtained in preliminary tests by the addition of the antihistaminic substance, all patients with a history of allergy were injected with Dijodon D. This meant a certain selection which might possibly have an unfavourable effect on the results recorded in the Dijodon D group.

b) *Results*

The results will be apparent from the following tables. The patients were divided into two groups. The first group comprised all those patients in whom no untoward reaction or only a feeling of warmth was recorded. Cases with a feeling of warmth without other symptoms were referred to this group, first because it is difficult for the examiner to judge it objectively, secondly, because the discomfort experienced by the patient is very slight. The second group comprises all those cases with other reactions such as cough, sneezing, nausea, vomiting, urticarial lesions, and shock.

Table 1

Contrast medium	Nr.	No reaction or feeling of warmth	Other reactions
Dijodon »Leo»	350	266	84 = 24 per cent
Umbradil »Astra»	150	112	38 = 25 per cent
Dijodon D »Leo»	500	469	31 = 6 per cent

In order to strengthen the validity of the observations made in the control group the latter was increased by a further number of patients on whom contrast medium identical with Dijodon but made by other manufacturers (Umbradil, Astra) was used. As will be apparent from the tables, the reactions in these two groups of controls were about the same. In the Dijodon D group, however, the incidence of the reactions was only one quarter of that recorded in the other groups.

Table 2

Nr. urographic examinations	250	300	350
Dijodon »other reactions»	55 = 22 %	72 = 24 %	84 = 24 %
Nr. urographic examinations	300	400	500
Dijodon D »other reactions»	18 = 6 %	24 = 6 %	31 = 6 %

Table II gives the distribution of the reactions observed. It shows that the reactions were fairly constantly distributed over the period of several months during which the investigation was carried out with various batches of contrast media.

Table 3

Nr. urographic examinations	Contrast medium	Nausea	Vomiting	Cough, sneezing etc.	Urticaria	Shock
350	Dijodon	52 = 15 %	16 = 4 %	11 = 3 %	4 = 1 %	1
150	Umbradil	22 = 14 %	6 = 4 %	8 = 5 %	2 = 1 %	
500	Dijodon D	23 = 4.6 %	2 = 0.4 %	2 = 0.4 %	4 = 0.8 %	

Table III gives the types of reactions seen in the various groups. It should be observed that in the Dijodon D group the reactions accompanied by a nausea feeling were much milder than in the control group. Allergic reactions such as sneezing, cough and urticarial lesions were observed also in the Dijodon D group, though only occasionally.

Discussion

It will be apparent from the above that the reactions to contrast medium deposited in the blood stream in connection with urography are by no means uncommon. The frequency and character of these reactions seem to justify a search for contrast media with fewer side effects. It is obvious that the administration of an antihistaminic substance simultaneously with the contrast medium essentially decreased the occurrence of reactions to intravenously injected contrast medium. Moreover, any reactions then seen were also less serious than those in the control group. It is also apparent that, as was expected from clinical experience, the antihistaminic agent was not able to control *all* allergic reactions.

The favourable effect of pre-medication with antihistaminic drugs was most prominent in cases in which one and the same patient had received injections of different contrast media at repeated urographic examinations. The series thus included, for example, a number of cases in which the patients, who were being followed up roentgenologically for renal tuberculosis etc., had had considerable trouble after the injection of ordinary contrast medium but felt no discomfort at all after the injection of Dijodon D. All those cases in which repeated injections were given with different media showed without exception that Dijodon D was followed by fewer untoward reactions than were ordinary contrast media.

Repeated injections of Dijodon D in one and the same patient had no effect on the tolerance of the patients to the contrast medium.

Observations made in the present investigation thus justify the incorporation of an antihistaminic drug in contrast medium or pre-medication with the drug. The prophylaxis of shock occurring in connection with injections of a contrast medium ought to include medication with some antihistaminic substance. A dose of 20 mg antihistaminic agent was found to be suitable. If, as is often the case in urography, the examination calls for a second injection of contrast medium, it may be given without any addition of antihistaminic agents. In examinations requiring a relatively large quantity of contrast medium, such as in angiocardiography, the amount of antihistaminic agent incorporated in the contrast medium should never exceed 20 mg or the patient should be pre-medicated in good time with some antihistaminic drug either by injection or per os.

SUMMARY

It is claimed that the frequency and nature of the untoward reactions to contrast medium deposited intravenously in connection with urography, for example, justifies a search for new contrast media. Antihistaminic substances were tried in the prophylactic

treatment of the untoward reactions to contrast media now available. Contrast media with an addition of antihistaminic agent (20 mg Benadryl in 20 ml Dijodon) were tried in urographical examinations of adults: no such addition was given to controls. The antihistaminic group showed fewer and milder untoward reactions to the contrast media than did the control group. This prophylaxis did not completely control all allergic reactions.

ZUSAMMENFASSUNG

Es wird der Anspruch darauf erhoben, dass die Häufigkeit und die Art der Folgeerscheinungen von intravenös gegebenen Kontrastmitteln wie z. B. bei der Urographie, das Forschen nach einem neuen Kontrastmittel rechtfertigen. Es wurden Versuche mit Antihistamin-Substanzen angestellt als prophylaktische Behandlung der Folgeerscheinungen nach den gegenwärtig verfügbaren Kontrastmitteln. Kontrastmittel mit einem Zusatz von Antihistamin-Stoffen (20 mg Benadryl in 20 ml Dijodon) wurden versuchsweise bei der urographischen Untersuchung von Erwachsenen verwendet: bei den Kontrollen wurde der Zusatz weggelassen. Die Antihistamin-Versuchsgruppe zeigte wenigere und gemilderte Folgeerscheinungen auf das Kontrastmittel hin als die Kontrollgruppe. Diese Prophylaxe vermochte nicht alle allergischen Reaktionen zu beherrschen.

RÉSUMÉ

L'auteur fait valoir que la fréquence et la nature des réactions défavorables causées par les substances de contraste introduites dans les veines, à l'occasion d'urographies par exemple, justifient la recherche de nouveaux produits de ce genre. Des corps antihistaminiques ont été essayés dans le traitement préventif des réactions malencontreuses déclenchées par les milieux de contraste dont on dispose aujourd'hui. Ceux-ci furent expérimentés avec adjonction d'un agent antihistaminique (20 mg de Bénadryl dans 20 cc³ de Dijodon) lors d'examens urographiques chez des adultes; les cas de contrôle ne reçurent pas cette adjonction. Le groupe à antihistaminiques réagit moins souvent et moins fortement aux substances de contraste que l'autre. Cette mesure prophylactique n'abolit cependant pas toutes les réactions allergiques.

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FROM THE UNIVERSITY INSTITUTE FOR MEDICAL RADIOLOGY, GENEVA, SWITZERLAND
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THE PROBLEM OF PREGNANCY IN HODGKIN'S DISEASE[1]

by

René Gilbert

Comparatively favourable forms of Hodgkin's disease treated by radiotherapy, as well as cases of full-term pregnancy occurring in this category of patients, have been more frequently reported during the last ten to twenty years.

The actual figures remain fairly modest, for the frequency of Hodgkin's disease is low; it represents an average of 5 ‰ autopsies in large cities (3.5 ‰ hospital patients) with a percentage up to 5.5 ‰ in 1936 at Basle (LÜDIN). According to several authors, the disease predominates in the male sex (personally we have observed nearly total equality between both sexes in over a hundred patients). Therefore, there seems to be little probability of any coincidence between pregnancy and Hodgkin's disease. Nevertheless this probability has increased since we now know far better how to diagnose and treat the favourable forms of the disease by roentgen rays. The main factors of success are, in our opinion: a) better knowledge of the clinical and anatomical manifestations of this eminently proteiformal disease; b) the necessity of abandoning fractional doses and interspaced irradiations, and the use of insufficiently penetrating rays; c) the necessity of a methodical administration of a sufficient dose *to destroy*, if possible from the first series of irradiation — as with malignant tumours — all granulomatous *foci* without damaging connective tissues, blood, and the general health of the patient. These ideas I have been defending, in practice and in literature, for over twenty-five years. The important increase of long remissions reported by numerous authors, and more frequent observation of full-term pregnancies in this category of patients, are no doubt the consequence of better knowledge of Hodgkin's disease and of the progress achieved in its treatment. We

[1] Paper read at the 6th International Congress of Radiology in London, July 1950; submitted for publication, Oct. 20, 1950.

have counted up to the spring of 1950 about 105 cases of full-term pregnancies, in 87 mothers;[1] there are probably many more.

This raises a *medical problem:* That of knowing what attitude should be adopted: 1st) in the event of the appearance of pregnancy in a Hodgkin's disease patient, or 2nd) in the event of the disease appearing a little before or during pregnancy.

Should we follow the authors who consider pregnancy as an aggravating factor, and *who advise interrupting it without discrimination?* (BLITZ, HERZ, HORSTER, DI PALO, SCHULTZ, etc.). *Or should we revise our ideas* in the light of present knowledge and therapeutic results?

I am in favour of this revision.

Does the observation of facts furnish us with a criterium? I think it does.

I have already[2] drawn attention to the important part of the evolutive potential of the disease to endeavour to explain the very dissimilar results of radiotherapy. Since then, the observation of facts confirms that this evolutive potential is the most determinating factor. If full pregnancy is rarely compatible with a rapid form of evolution (under 2 years), it is compatible as a rule with average chronic forms (2 to 6 years) and with particularly slow forms (over 6 years). This is especially so in the cervico-thoracic region where there are no marked constitutional signs, *on condition that* roentgen therapy is technically correct and well carried out.

I have personally observed thirteen cases of full pregnancy in nine mothers (*biopsy* in eight cases). Twelve times (eight mothers) pregnancy appeared in patients free from symptoms after roentgen therapy. *In every case*, pregnancy evolved normally without detriment to the mother. None of the eight mothers succumbed from any aggravation caused by pregnancy. There were four deaths of which three[3] occurred from 2 to $3^1/_2$ years after confinement; four are still living (*average time* of survival for the *eight* mothers = twelve years after beginning of roentgen therapy).

[1] Counting the ten cases of pregnancy published by J. BICHEL just before the London Congress (see *Acta radiol.* 33 (1950), 427).

[2] Fifth International Congress of Radiology, Chicago 1937; see Am. J. Roentgenol. 41 (1939), 198.

See also Acta radiol. 15 (1934), 508. (International Congress of Radiology, Zurich, paper presented together with my former collaborators L. BABAIANTZ and S. KADRNKA.)

[3] The fourth death occurred one year after the confinement of a first pregnancy, and one month after the premature confinement at the eighth month of a second pregnancy which appeared at the time of a serious relapse; it was the case of a doctor's daughter. We have observed another case of two pregnancies in a woman who was both a doctor's daughter and a doctor's wife. In each case, the mother in the beginning was able to feed her child. This shows how difficult it is to give advice which is followed.

All the *children* are normal in their phenotype; their ages run from 24 to 5 years (five males, eight females).

The ninth mother (thirteenth pregnancy) showed the first symptoms of the disease during the eighth month of pregnancy: we shall consider the problem of this particular case further on.

Thus nearly all my personal observations concern mothers free from symptoms after roentgen therapy, in whom pregnancy occurred (12 full pregnancies). But we must also take into account two other categories of cases, to which the ninth mother, and the one who succumbed a short time after premature confinement during a second pregnancy, belong. PAPILLON and CHAVANNE, in a recent publication,[1] very rightly distinguish between:

1) *Pregnancy* occurring *during an evolutive period* of the disease.
2) *Pregnancy* occurring *during a period free from symptoms* after roentgen therapy.
3) *Hodgkin's disease* appearing clinically for the first time during pregnancy.

These authors, who confirm the conclusions drawn in my former publications, grouped 12 cases in Lyons (France) and neighbourhood, *plus* 48 cases in literature, *i. e.* 60 cases which were spread over the three above mentioned categories. Their analysis leads to the following conclusion:

1) Pregnancy in a period free from symptoms: no influence whatsoever on Hodgkin's disease.

2) Pregnancy in an evolutive period: frequent relapses during the first six months of gravidity or during the post-partum, but without marked influence on the course of the disease.

3) Hodgkin's disease having appeared during pregnancy or post-partum: nearly always rapid, feverish course, reacting badly to roentgen therapy, and having a short survival time (not exceeding an average of 18 months).

Nine cases noted by PAPILLON and CHAVANNE belong to the latter category: five had a recrudescence of the disease between the third and sixth months, the four others in the *post-partum*. On this subject, the Lyons' authors recall the possible influence of a hormonal factor (first mentioned in England by GEMMEL), as the aggravation noted generally corresponds to the two hyperfolliculinaemia phases.

We also note in FABIAN'S[2] thesis that out of twelve cases of this category, nine maternal deaths occurred principally during the weeks

[1] J. PAPILLON et G. CHAVANNE, in *Journal de Médecine de Lyon*, 31 (1950), 127. — See also G. CHAVANNE, *Thèse* de Lyon, 1948—1949.

[2] D. FABIAN, *Thèse* de Halle, 1943.

or months following child birth (but note that a similar case of HERZ, and two of GEMMEL's and SALVINI's survived longer).

In this third category, I examined a patient (the ninth mother) who developed Hodgkin's disease in the eighth month of pregnancy (cervico-thoracic form); the course of the illness seemed benign. I treated this patient by roentgentherapy after post-partum: the effect in this case was very favourable. Eight years of clinical cure have now elapsed since this time. Four years ago, in spite of flourishing health, this patient underwent without my knowledge medical abortion, and sterilization, for two further and contiguous pregnancies! In my opinion, such decisions are no longer defensible nowadays in cases of this category.

What should be done when there is coexistence of pregnancy and Hodgkin's disease?

1) One fact seems to be established: that pregnant women, who have suffered from relatively mild forms of »Hodgkin», *and free from symptoms after roentgen therapy*, show a remarkable faculty in standing pregnancy. In cases of this category I am of opinion that we should *formally reject the indication* for an interruption of pregnancy.[1]

2) If pregnancy takes place in a *period of evolution*, it becomes a case for individual judgement. Likewise, if the disease appears for the first time during pregnancy, particularly during the first six months. In both these groups, radiotherapy should be tried, unless an abdominal or inguinal situation should necessitate irradiating the product of conception during the first six months. Even in alarming evolutive forms *quoad vitam*, the treatment often enables one to save the child, without the course of the illness being noticeably affected. In these cases the benefit that one believes one can obtain for the mother by interrupting pregnancy, generally turns out to be a vain hope.

3) It is advisable not to permit nursing, although the latter has been noted in several cases to be without bad effect.

What answer may we give if a patient suffering from Hodgkin's disease seeks advice as to whether he or she should marry or have children? The matter is a delicate one, especially if the patient be a woman. I was formerly of the opinion to advise people not to marry or to have children; I now have a milder outlook: it is wise to advise woman suffering

[1] PAPILLON and CHAVANNE propose considering women »en rémission franche» (free from symptoms) who for at least six months have all the characteristics of apparent health, without clearly perceptible nodes nor other symptoms related to the disease. We are of opinion that that may be correct for the purposes of classification: but should a pregnancy appear during the six first months, we think that the physician's clinical sense must prevail. We must consider the location, the evolutive character of the particular case, as well as the time between the appearance of the first symptoms and the beginning of the treatment.

from Hodgkin's disease not to marry; or, if marriage takes place, not to have children. However, if the interested parties insist on marrying and having children, the physician may give his consent in clearly localised cervico-thoracic forms without marked constitutional signs, and which have reacted well to radiotherapy. The future husband should be duly warned, of the risks he is taking.

Up till now, descendants — those mentioned in medical literature and our own cases — have been free from the disease (the solitary case of PRIESEL and WINKELBAUER is a contestable one). Children develop normally in their phenotype. The oldest cases that I have observed are respectively twenty-four and twenty-three years of age; the eleven others range over ages down to five years. Their photographs together with those of their living mothers have been shown at the Congress.[1]

SUMMARY

The author notes that the number of long remissions (free from symptoms) after roentgen therapy is increasing in Hodgkin's disease, as well as in the cases of full pregnancy appearing during the course of the disease. He gives the reasons for this and briefly describes his own cases (13 full pregnancies in nine mothers since 1926; 13 descendants, living, and in good health). Based on his own experience and on the cases published by several authors, the author gives his opinion on the line of action to be followed, when there is coincidence of pregnancy and Hodkin's disease, with distinctions in certain cases. It is suggested that the evolutive potential is the most important determinating factor.

ZUSAMMENFASSUNG

Der Verfasser stellt fest, dass bei der Hodgkinschen Krankheit die Anzahl langer Remissionen (Symptom-Freiheit) nach Röntgentherapie zunimmt, wie es auch an den Fällen von ausgetragener Schwangerschaft im Verlaufe der Krankheit zum Ausdruck kommt. Er gibt die Gründe dafür an und beschreibt kurz seine eigenen Fälle (13 ausgetragene Schwangerschaften bei neun Müttern seit 1926; 13 Lebend-Geburten, völlig gesund). Der Verfasser, der sich auf seine eigenen Erfahrungen und die von verschiedenen Autoren mitgeteilten Fälle stützt, gibt sein Urteil über die Massnahmen ab, die bei gleichzeitigem Bestehen von Schwangerschaft und Hodgkinscher Krankheit befolgt werden müssen, bei besonderer Berücksichtigung bestimmter Fälle. Es wird angenommen, dass das Evolutionspotential der wichtigste, weil entscheidende Faktor ist.

RÉSUMÉ

L'auteur constate, d'après la littérature, que le nombre des longues rémissions après roentgenthérapie augmente dans la maladie de Hodgkin; de même, les cas de grossesse à terme survenant au cours de la maladie. Il en donne les raisons, et fait brièvement part de ses cas personnels (13 grossesses à terme chez neuf mères depuis 1926; 13 descendants vivants et bien portants). Sur la base de son expérience, et des cas rassemblés et étudiés par plusieurs auteurs, il exprime son opinion sur la conduite à tenir, du point de vue médical, lorsqu'il y a coïncidence de grossesse et de maladie de Hodgkin, en faisant une distinction entre les cas qui peuvent se présenter. Il considère le potentiel évolutif de la maladie comme le facteur déterminant le plus important.

[1] The author will develop this subject with documentation in the near future in the *Journal de Radiologie et d'Electrologie* (Paris).

FROM THE RADIUM CENTRE IN ODENSE, DENMARK (DIRECTOR: PAUL JACOBY)

STILBOESTROL IN THE TREATMENT OF CARCINOMA OF THE PROSTATE[1]

by

Mogens Roelsgaard

Owing to the difficulties connected with the early diagnosis of carcinoma of the prostate, the majority of cases are too far advanced for radical surgery, when they arrive for institutional treatment.

According to earlier statistics (YOUNG) only 10 % of the patients with carcinoma of the prostate gland were operable when admitted to hospital. Therefore, palliative therapy is usually the only possible procedure. Hormone therapy, in the form of castration or administration of oestrogenic hormones, appears to have made life more endurable for these patients and it probably also contributes to prolonging their lifetime.

Diagnosis

Some disagreement still exists as to the incidence of prostatic carcinoma. According to autopsy materials (ROMANUS) it would appear to be a very common lesion, malignant changes of the prostate having been found in up to 30 % of men above 40—50 years of age. Clinicians, on the other hand, report a lower incidence. YOUNG reports carcinoma of the prostate in about 20 % of patients exhibiting symptoms of prostatic hypertrophy. It is beyond doubt that numerous cases remain unrecognized as malignancy, following a course without particularly marked symptoms, characterized mainly by moderate urinary obstruction and pain suggesting rheumatism over the loins and hips.

In addition to rectal examination which is not very reliable in the early stages because the changes in the prostate are still slight, biopsy affords a diagnostic possibility. Even the latter method has not given particularly brilliant results. The safest procedure is perineal biopsy

[1] Submitted for publication, Aug. 22, 1950.

(NÆRÅ) which, however, appears to give positive results in only 50 per cent of the cases (BARRINGER). Transurethral biopsy is even more rarely successful, since this route does not afford a satisfactory approach to the posterior lobe where the carcinoma is considered to originate in most cases.

Urethrography with opaque medium also affords a possibility of making the diagnosis. The urethral changes appear in the form of stiffness and narrowing of the lumen in the prostatic portion and absence of contractions in the urethra (KNUTSSON).

During recent years the Papanicolaou technique has also been utilized in the efforts at making an early diagnosis. By this method HERBUT & LUBLIN, in 1947, demonstrated cancer cells in prostatic secretions in 17 out of 100 cases in which the palpatory findings were suspicious. In later stages of prostatic carcinoma it is stated to be difficult to obtain secretion because of obstruction of the prostatic ducts or diffuse hardening of the prostate.

In most cases, however, the diagnosis is not made until metastases have appeared and the patient presents roentgen evidence of bone metastases as well as an increase in the acid serum phosphatases.

Normally the activity of acid phosphatases in the prostate is 100 times that of any other tissue. Following removal of biopsy or following severe manipulation, a brief increase in acid serum phosphatases has been found in cases of benign hypertrophy of the prostate. The explanation has been advanced that phosphatases from the prostatic secretion have entered the blood stream through the ulceration resulting from the punch biopsy. In the same way the increase in serum phosphatases should be possible, when the carcinoma forces its way through the prostatic capsule.

Acid phosphatases are also produced in bone metastases, a process which further increases the serum phosphatases. The normal value of acid serum phosphatases is considered to be 3 units of phosphatase per 100 cc of serum or less, measured according to the King-Armstrong method, modified by Gutmann. If the value exceeds 3 units, it is interpreted as pathological and more than 5 units very much suggests metastasization of prostatic carcinoma. If the values exceed 10 units, the presence of bone metastases is considered proven (WRAY, 1945). When the prostatic cells have undergone marked destruction, no acid phosphatases are formed, and consequently the serum phosphatases are not raised.

Treatment

The treatment depends on the stage at which the lesion has been diagnosed. With a proven diagnosis and in the absence of any signs of

invasion of the prostatic capsule or metastases, perineal prostatectomy may be considered. According to YOUNG and BARRINGER this procedure carries a mortality of 5—10 %. They were able to report a 50 % 5-year cure rate. Other methods of treatment can be but symptomatic. Among them hormone therapy and roentgen irradiation are most important.

By animal experiments HUGGINS (1941) was able to demonstrate that increased activity of the androgenic hormones was related to the development of prostatic carcinoma. He found, moreover, that in cases of prostatic carcinoma, administration of oestrogenic hormones reduced the production of androgenic hormones by inhibiting the gonadotropic hormones of the anterior pituitary.

Hormone therapy would appear to be preferable to castration, since the former also inhibits the production of androgenic hormone in the adrenal cortex. Follow-up studies appear to show that the results from both methods are almost identical (BUMPUS, EMMET).

The most effective dosage of stilboestrol is generally considered to be 10—15 mg daily (HUGGINS, ANDERSEN). Doses of *e. g.* 50—100 mg daily have proved less effective. It is even claimed by some workers (PERRIN, 1946) that quantities in excess of 2—5 mg daily are of no effect.

In a follow-up study of patients treated with stilboestrol, HUGGINS (1949) found that 55 % had a recurrence of pain within 2 years and that 75 % had died within 5 years of the onset of treatment. Among 50 patients treated with oestrogenic hormone, HECKEL (1948) reported 22 survivors in good health from 6 months to 5 years after the time of diagnosis.

In cases of especially painful bone metastases, hormone therapy is combined with roentgen irradiation.

Among the untoward effects of stilboestrol, growth of breasts is most common. Clinically, the changes resemble gynæcomastia. According to HUGGINS, stilboestrol has in a few cases been followed by mammary malignancy.

Other side-effects of stilboestrol are oedemas of the legs due to retention of sodium and chloride which reduces the excretion of water. Some patients complain of dyspeptic symptoms. Moreover, liver damage has been reported in a few cases (WATTENBERG 1946, KLØVSTAD 1949). Stilboestrol is considered contra-indicated in the presence of liver disorders, since the hepatic function is of decisive importance to the metabolism of stilboestrol. Furthermore, an accumulation of fat may appear at the site of the mons pubis, and cessation of testicular function is a natural consequence of stilboestrol therapy.

Writer's Series

From 1933 a total of 91 patients with carcinoma of the prostate have been treated at the Radium Centre in Odense. Of them 49 have received stilboestrol which has been used since the spring of 1945. The diagnosis was confirmed histologically in only 30 out of the 91 cases. In the remaining 61 cases it was based on the clinical findings and roentgen evidence of bone metastases.

One of the objects of this follow-up study was to compare the duration of the relief from symptoms and the survival time of the patients treated prior to 1945 by roentgen only and of those treated after 1945, all of whom received stilboestrol. In order to obtain a uniform material the author included only those patients who had exhibited bone metastases. This is tantamount to a series comprising exclusively inoperable cases in which stilboestrol is of most use.

In practically every case the bone metastases were found to be of osteoplastic nature, showing marked sclerosis of the bony tissue which is typical of metastases from prostatic carcinoma. Osteoplastic metastases may, however, occur also in mammary carcinoma and, more rarely, in thyroid carcinoma and hypernephroma. These lesions could be ruled out in the present cases.

Metastases in the bones were found in a total of 66 patients 30 of whom received roentgen therapy only. Among the remaining 36 cases 19 received roentgen as well as stilboestrol therapy, whereas 17 received stilboestrol only. Histological verification was available in 18 out of the 66 cases, but all the patients exhibited typical prostatic changes and unmistakable bone metastases.

Age Distribution. As had been expected there is a marked predominance of cases after 60 years of age. In the 2 groups there were 18 and 17 patients respectively between 60 and 70 years of age and 4 and 16 respectively between 70 and 80 years of age. Only 7 and 1 respectively were in the age group 50—60, and only 1 patient was younger than 50, when the treatment was started.

Symptoms. The most common complaint was difficulty of urination of a character like that of benign prostatic hypertrophy. This applies to 32 patients, 17 and 15 in each group. In 29 cases (14 and 15) pain was the cardinal symptom, either in the form of painful urination or pain in the loins, radiating to the lower limbs. Hæmaturia was an early symptom in only 2 cases, whereas 7 patients (5 and 2) complained of constipation at a rather early stage of the disease.

The interval from the appearance of the first symptoms until admission to hospital ranged from 6 months to 1 year in 26 cases (11 and

15), whereas 18 (9 and 9) had had symptoms for less than 6 months. Symptoms had been present for more than 1 year before admission to hospital in 17 cases (10 and 7).

A total of 12 patients (6 in each group) had experienced acute retention of urine prior to treatment, and 10 patients (6 and 4) had undergone prostatectomy before receiving roentgen or stilboestrol therapy.

Treatment. As mentioned above, the first group of patients received only roentgen therapy. The standard treatment was irradiation of the prostate, 1,200 to 1,600 r to 3 fields, one over the symphysis pubis, one over the sacral bone, and one directed at the perineum. The size of the fields was 10×15 cm over the symphysis and the sacral bone and 8×10 cm in the perineum. The patients received irradiation of 1 field daily, 240 r at a time, and the course therefore lasted from a fortnight to 3 weeks.

In cases of persistent pain or recurrence of pain, irradiation was later directed at the sites of the pain, *e. g.* the lumbar column or other sites, where metastases were demonstrable.

Stilboestrol therapy was started in hospital. The dose was 15 mg of stilboestrol daily, 5 tablets being given 3 times daily. This dosage was continued while the patients remained at the Radium Centre, for 3 to 4 weeks according to the rate at which they were relieved of symptoms. After discharge the patients continued the course at home, taking 3, 6, or 9 tablets daily, all according to their condition and side-effects, if any. Two months after discharge they appeared for re-examination and were thereafter seen every third month during the first year and later at intervals of up to 6 months.

In the 19 cases where stilboestrol was supplemented by roentgen irradiation, the latter was administered in the form of the above-mentioned standard treatment or directed at the vertebral column or pelvis in cases of severe metastatic pain. During the last few years it has been endeavoured to use stilboestrol alone, and this was the only treatment received by 17 patients.

Untoward Effects of Stilboestrol: These were, on the whole, slight. The most common complaint was mammary hypertrophy accompanied by tenderness. In a few instances the hypertrophy was rather pronounced and the palpatory findings so suspicious that a biopsy was removed. In every case microscopical examination showed gynæcomastia and never malignancy. Twelve patients showed unmistakable growth of breasts and 5 of them were greatly troubled by tenderness. In only one case did the mammary changes necessitate temporary interruption of the treatment.

Dyspepsia consisting in nausea and epigastric pressure was reported by 7 patients, so severe in two that they stopped taking the tablets.

Oedemas of the lower limbs occurred in 7 cases.

Other untoward effects were not observed, and there was no case of hepatic changes or exanthema.

Results of Stilboestrol Treatment. The duration of the relief from pain after roentgen treatment only and after stilboestrol are compared in Table 1. It will be seen that in 22 cases of the former group, pain recurred within 3 months. In the second group only 8 patients had a recurrence of pain within this period. Within 6 months 17 patients of Group 2 (about 50 %) had a recurrence of pain. At this time 29 out of 30 patients in Group 1 had pain. Eleven patients of Group 2 got on without pain for more than one year after the treatment was started. Of them 7 had received stilboestrol only. Three patients of this group enjoyed a painless interval of more than 2 years. In Group 1 only one patient remained free of pain for 2 years.

Table 1.

Duration of relief from pain after treatment.

Number of months	Patients treated with		
	roentgen	roentgen + stilboestrol	stilboestrol
0— 3	22	5	3
3— 6	7	4	5
6— 9		4	2
9—12		2	
12—15		3	1
15—18		1	2
18—21			1
21—24			
24—27	1		2
27—30			
30—33			
33—36			1
	30	19	17

Like the pain, the difficulty of urination yielded more rapidly to stilboestrol than to irradiation. There was a marked improvement in the general condition, increased hæmoglobin content, and the patients gained weight.

In 15 instances the course of stilboestrol was followed by undoubted diminution of the prostate. This occurred chiefly in those cases who had shown pronounced enlargement of the prostate prior to treatment.

Seven patients of Group 1 gradually developed paresis of the lower limbs, presumably due to the invasive growth of the carcinoma into

the true pelvis. Paresis of the lower limbs occurred in only one case of the group treated with stilboestrol.

In 4 cases of Group 2 there was roentgen evidence of regression of the bone metastases and in one case they had yielded completely to stilboestrol. No such regression was demonstrable in the cases who received only roentgen radiation.

Effect on Acid Serum Phosphatases. In 12 instances the acid serum phosphatases were normal (less than 3 units per 100 cc of serum) before the treatment and in 19 enhanced. Of the latter 5 had more than 10 units. Table 2 shows the changes in each individual case after stilboestrol treatment. Among the cases with normal pre-treatment values, two showed an increase up to more than 3 units and one up to more than 10 units. In the other nine cases the values remained normal.

Table 2.

Effect of stilboestrol on acid serum phosphatases.

Before Treatment		After treatment		
Phosphatase	Patients	Less than 3 units	Between 3 and 10 units	More than 10 units
Less than 3 units	12	9	2	1
Between 3 and 10 units..	14	8	5	1
More than 10 units	5	1	3	1
	31	18	10	3

In 5 instances the acid serum phosphatases were not followed.

Among the 14 patients showing pre-treatment values from 3 to 10 units, there was a return to normal in 8, whereas among the 5 patients with values exceeding 10 units, a reduction occurred in 4, in one even down to normal.

A study of the acid serum phosphatases in 14 survivors showed that 7 with values in excess of 5 were in great pain and in poor general health, whereas out of 7 patients with normal acid serum phosphatases only one was in a poor condition.

Survival Time. In the first group, eight out of 30 were surviving at the end of one year. Within 2 years all the patients of this group had died. Among 30 patients of Group 2 who had been started on stilboestrol during the period 1945—1948, 20 survived for more than one year. At the end of two years 15 patients of this group (50 %) were still alive.

It was tried also to include cases of prostatic carcinoma without demonstrable metastases in the bones (stated in brackets in Table 3).

Table 3.

Survival time.

The figures in brackets indicate the total number of cases treated for prostatic carcinoma.

Year	Number of patients	Survival time after treatment			
		More than 1 year	%	More than 2 years	%
1933—44	30 (40)	8 (10)	27 (25)	0 (0)	0 (0)
1945—48	30 (41)	20 (28)	66 (68)	15 (22)	50 (53)

This does not result in a definite shift in the survival time within the two groups, but the relation of the survival time in the two groups is the same as previously. As stated above, the groups were extremely uniform with respect to the duration of symptoms before treatment and the spread of bone metastases.

Conclusion

In carcinoma of the prostate with bone metastases, stilboestrol therapy appears to result in longer relief from pain than roentgen irradiation alone. The general condition also was better in the cases receiving stilboestrol.

There was a marked difference in the survival time of the patients treated with roentgen and those treated with stilboestrol, although the results of this series must be accepted with a certain reserve, because of the small numbers involved.

It is worth mentioning that paresis of the lower limbs was less common among the patients who received stilboestrol than among those who received only roentgen irradiation.

In cases of very persistent pain due to bone metastases, the best results appear to be obtained by a combination of stilboestrol and roentgen rays.

SUMMARY

After reviewing hormone therapy in carcinoma of the prostate gland the author presents a series of cases with bone metastases, 30 of whom received roentgen irradiation and 36 stilboestrol supplemented in some instances by roentgen. The results of the two forms of treatment are compared and discussed.

Stilboestrol proved to be of an excellent palliative effect which lasted longer than that of roentgen radiation alone. Furthermore, the survival time was longer after stilboestrol than after roentgen therapy.

ZUSAMMENFASSUNG

Nach einem Überblick über die Hormontherapie bei Prostata-Carcinom veröffentlicht der Verfasser eine Anzahl Fälle mit Knochenmetastasen. Von diesen erhielten 30 Röntgenbestrahlungen und 36 Stilboestrol, in besonderen Fällen mit dem Zusatz einer Röntgenbestrahlung. Die Ergebnisse beider Behandlungsformen werden verglichen und überprüft. Stilboestrol zeigte eine ausserordentlich gute palliative Wirkung, die länger anhielt als die alleinige Röntgenbestrahlung. Ausserdem war nach Stilboestrol die Überlebensdauer länger als nach der Röntgentherapie.

RÉSUMÉ

L'auteur fait d'abord une revue du traitement hormonal du cancer de la prostate, puis présente une série de cas compliqués de métastases osseuses, dont 30 furent irradiés aux Rayons Rœntgen et 36 reçurent du Stilbœstrol, avec, certaines fois, adjonction de radiothérapie. Il compare et soumet à discussion les résultats des deux formes de traitement.

Le Stilbœstrol s'est montré doué d'une excellente action palliative, plus durable que celle des Rayons Rœntgen employés seuls. En outre, la survie, après traitement par le Stilbœstrol, a été plus longue qu'après la radiothérapie.

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